Lifesavers for millions
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Editiones Roche
Basel
Content

6 Foreword

8 Introduction

14 Isoniazid (Rimifon): first specific against tuberculosis
by Sabine Päuser

78 Bactrim
by Christoph Mørgeli

140 Rocephin
by Urs B. Schaad

186 About the authors
Sixty years ago Roche’s research department produced the first drug effective for pulmonary tuberculosis: Rimifon. Even now its active ingredient, isoniazid, remains an indispensable component of tuberculosis treatment. Sixteen years later Roche introduced Bactrim for the treatment of bacterial infections. Its ingredient, co-trimoxazole, composed of two active substances, has since been administered in about two billion doses. Inexpensive and versatile, Bactrim and its generic forms have become a standard treatment for infection, particularly in developing countries. Thirty years ago Roche brought the cephalosporin antibiotic Rocephin to market. This product too, which is indicated in a particularly wide range of infectious diseases, has since benefited millions of patients.

Matthew White, author of Atrocitology: Humanity’s 100 Deadliest Achievements calculates that all the wars from 2500 years of human history have claimed around 455 million lives. By contrast, the above three remarkable anti-infectives from Roche have helped to save several billion human lives.

Today we’re apt to take such therapeutic mainstays for granted, often forgetting that they wouldn’t have been discovered, much less have reached the market, without investors who had the courage to invest in modern pharmaceutical research, and wanted to see a return on their investment. In the case of the three products in question, this is all history, and all three are now available as generics from many suppliers at a small mark-up on the production cost. The research achievements made possible by courageous investors now benefit huge segments of the global population. Faced with increasing resistance to antibiotics, we remain dependent on a research-based pharmaceutical industry dedicated to developing new products that can not only match but improve on current therapeutic outcomes.

The double anniversary of Rimifon and Rocephin is a good time to look at the history and current value of these three anti-infectives. Each had its own hurdles to cross on the way to becoming a pharmaceutical classic. In each case it was immensely talented scientists who made success possible. Roche provided them with an environment in which they could thrive. Very importantly, the beneficiaries of the medical advances they ushered in include patients in developing countries. This book illustrates with real-life examples how the pieces, players and factors involved in drug development fit together.

Dr Gottlieb Keller
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The discovery and development of new drugs and treatments is an extremely expensive and protracted undertaking. Development costs can now total between 500 and 1000 million Swiss francs ($525m–$1050m) or more, depending on the indication. Development takes between eight and twelve years. At the same time, drugs can be copied very easily and quickly because their composition has to be declared. For investments in drug research and development to pay off, they have to be adequately protected, which is where patents come in. Patents temporarily confer an exclusive right to market the products they protect. Cheaper generics cannot be put on the market until the original products go off patent.

Patents are granted for a 20 year term from the filing date. Patents for new drugs can be extended for up to five years depending on how long a drug took to develop. Because patents need to be filed at a very early stage in development, the effective patent term – the interval between market introduction and patent expiry – averages 13 to 14 years. In developing and emerging-market countries such as Brazil, China, India and Mexico, patents cannot be extended. And because new drugs reach these markets later, the effective patent term there is only around six to eight years.

Since patents are the only means of securing temporary market exclusivity, they are immensely important for a research-based drug company like Roche. In a way, they are the backbone of our business model.

This was not always so. The importance of patents has increased steadily over the last 40 years. And during this period the regulatory environment has undergone huge changes that have facilitated the emergence of a strong generics industry.

Changes in the patent system

Switzerland acceded to the European Patent Convention (EPC) on October 7, 1977 and in the process adopted ‘product protection’ for chemical compounds, including active pharmaceutical ingredients. Product protection makes it possible to patent active substances as such. A product patent confers comprehensive protection that is independent of the manufacturing process, formulation or use.

Before joining the EPC, Switzerland, like many other countries, only allowed manufacturing processes for active substances to be patented. This caused the industry to invest heavily in the research and development of manufacturing processes that would maximize the protection afforded to the substances manufactured. The aim was to prevent generics companies from developing unpatented manufacturing processes. During the 1980s an increasing number of countries introduced product protection, often in the course of concluding free trade agreements in which the USA played a leading role. In the Uruguay round of the General Agreement on Tariffs and Trade (GATT) negotiations, the World Trade Organisation was then set up on April 15, 1994 in Marrakech, Morocco. An integral component of the agreement was the Trade-Related Aspects of Intellectual Property Rights (TRIPS) agreement which laid down globally applicable standards for various intellectual property rights, including product protection for active chemical and pharmaceutical ingredients.

Least developed countries are not yet required to comply with these standards. The current transition period for compliance ends in 2016, but is likely to be extended further. Emerging-market countries, on the other hand, such as China, India and Brazil, have been required to implement these standards in legislation. India was the last of these countries to comply, implementing product protection for active pharmaceutical ingredients on January 1, 2005.

Changes in the regulatory environment

At one time, generic development couldn’t begin until the original product went off patent. Also, generics manufacturers were unable to refer to the original manufacturer’s registration documents when seeking approval for their products, but rather had to submit their own registration dossiers. In other words, they had to conduct clinical trials, even if the documentation in question did not, until the late 1960s, have to meet particularly high standards.

Today generics can be developed even before the original product’s patent expires. The authorisation application can also

1 Italy likewise introduced product patents when it joined the EPC, on 1 December 1978. Germany had recognised product protection since 1968. The USA was the only country where it had been possible to patent drug substances from the start.

2 Bioavailability is a pharmacological measure for the percentage of an administered drug that is available in the bloodstream. By definition, the bioavailability of intravenously administered drugs is 100%.
refer to the original manufacturer’s registration documents. It need merely be shown that the generic’s bioavailability is similar to that of the original product. Nowadays, generics are brought onto the market virtually on day 1 after patent expiry.

The revenue losses associated with patent expiry used to be more moderate than they are today, as two examples show.

Figure 1 shows the US sales (in millions of US dollars) achieved with Valium in the years 1981 to 1992. At the time Valium was Roche’s best-selling drug. The US patent for Valium expired in February 1985. The first generics appeared on the market about a year later. While US sales in the peak year of 1985 totalled $755m, they declined to $350m in 1986 and $210m in 1987.

Today’s revenue losses are much more drastic, as can be seen from Figure 2, which shows the sales (in millions of Swiss francs) achieved in the USA with Rocephin in the years 2000 to 2006. The patent expired in mid-July 2005. The first generics hit the market a day after patent expiry and Roche sales collapsed completely. This last example is particularly impressive evidence of the impact of patent expiry. It shows very clearly why strong, solid patents are so important to research-based pharmaceutical companies. To stay in business, Roche must not only renew, but expand its entire product portfolio with patented and innovative new drugs and therapies on average about every 10 years. Innovation is a must.

In the present environment, two factors drive medical progress: a patent system that creates conditions for investing in the discovery and development of new drugs and therapies and the existence of a generics industry that compels research-based companies to innovate.

Isoniazid, co-trimoxazole and ceftriaxone

The patent histories of the three anti-infectives described in this book – isoniazid, co-trimoxazole and ceftriaxone – couldn’t be more different.

Isoniazid, the active substance that Roche brought onto the market as Rimifon, was known long before it was found to be effective against tuberculosis. Even if product protection had been available in the early 1950s, isoniazid could not have been patented, simply because it was no longer new. Novelty is mandatory for patentability. Moreover, since various manufacturing processes were already known, there was no way of achieving anything like effective protection even with process patents. The result was of course that several companies quickly entered the isoniazid market, predictably forcing prices downward.

An unpatented agent like isoniazid would probably not be developed today. While data exclusivity – known in Switzerland as ‘first-applicant protection’ – also exists as an additional tool,
this does not actually confer market exclusivity. In the European Union and Switzerland the data protection period is ten years for an active substance first developed as a drug. In most cases this is markedly shorter than patent protection. There is no protection when an entirely new indication is found for a known active substance. First-applicant protection means that for ten years after first authorisation, the health authorities will not issue any further licenses based on the original manufacturer’s data. Outside Europe this protection is either unavailable or too short to ensure a sustainable business. First-applicant protection would have to be made more attractive worldwide and also extended to new indications, which require extensive clinical trials. Only then would it be attractive enough to develop an unpatented active substance such as isoniazid or a completely new indication for a known active substance.

Co-trimoxazole was jointly developed by Roche and Wellcome. Roche has been marketing co-trimoxazole under the brand name Bactrim since the early 1960s. This contains a combination of two active substances, sulfamethoxazole and trimethoprim. The drug combination had already been described as such in the literature, and so could no longer be patented. Sulfamethoxazole was also a well-known active substance and no longer eligible for patent protection. With trimethoprim the situation was different. On 10 November 1953 Burroughs Wellcome was granted a US patent on the drug substance itself. The patent expired in November 1970. Inside and outside the USA Roche and Wellcome managed to build up a relatively thick patent portfolio that giving them exclusivity in a number of important markets.

Ceftriaxone was invented in Roche laboratories and marketed under the brand name Rocephin from the early 1980s. It was filed for patent worldwide in 1979 and enjoyed product protection in all major markets. The Roche patents expired worldwide in 1999. However, patent protection continued in the USA until mid-July 2005. This patent belonged to Hoechst and was broad enough to include the active substance ceftriaxone. It had actually been filed before the Roche patents, but only granted much later, in 1988. Since US patents at the time had a term of 17 years from the date of grant, product protection for this drug did not expire until mid-2005. Roche was granted an exclusive licence under this patent.

All three products are today available as low-cost generics and they all feature on the WHO Model List of Essential Medicines. These innovative products are still benefiting patients today.

Once put onto the market by Roche as medical innovations, they continue even now to save lives daily thanks to their wide availability.

Dr Eric Notegen
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Isoniazid (Rimifon): first specific against tuberculosis

Sabine Pläuser
‘It has often been said that ‘man is his own worst enemy.’ This may or may not be true but it is certain that he has other enemies that vie with him for the title. One of the most pernicious of these and one which has plagued him since the dawn of history and beyond, is tuberculosis. It is not commonly realized that this ‘white plague’ of olden days, this unremitting decimator of human populations all through the Middle Ages, is still one of the principal causes of death today. Actually tuberculosis is responsible for more deaths of persons between 15 and 45 years of age than any other cause.¹

Herman Herbert Fox, 1953

Sometimes the time is so ripe for a particular discovery that the pressure to translate it into a practical blessing for mankind becomes immense. In such cases there are often many researchers at different locations across the world, who come up with the solution independently of one another, albeit in familiarity with each other’s work. Yet rarely are discoveries made so concomitantly as in the case of isoniazid, the first drug specifically targeting tubercle bacilli, which researchers from Roche, Squibb and Bayer came upon in rapid succession, one after the other.²

Rarely too does the solution of a medical problem generate such euphoria as this antituberculous drug, which even 60 years after its discovery continues to save many lives, albeit in combination with other drugs.

But rarely too in the mid-20th century was a cure so desperately needed, and so sought after, as for tuberculosis, an infectious disease that plays havoc with mankind whenever immunity is needed, and so sought after, as for tuberculosis, an infectious disease that plays havoc with mankind whenever immunity is weakened by hunger and destitution.

Tuberculosis researchers were under no illusions as to what the Second World War would bring in its wake: a fresh surge in infectious disease from the disease, and one not simply confined to Europe. In today’s Western Europe we have virtually forgotten the danger that this infectious disease once represented. Tubercle bacilli are spread through the air. Unlike many other pathogens, notably the flu viruses, they do not change their surface.³ Components of the immune response – coughing and sneezing – propel infectious droplets from person to person. When patients with open tuberculosis cough, without wearing appropriate prophylaxis such as a mask, they expel an infectious aerosol into ambient room air containing mycobacteria that may then remain viable for hours.⁴ Just ten bacilli are thought sufficient to cause a primary infection.⁵ Tubercle bacilli replicate slowly. Once they reach the bloodstream – usually starting from the lung – they are able to lodge in, and erode, almost any body organ. Death begins to become ineluctable once the immune system and/or drugs fail to keep the pathogen in check. Not for nothing did our forebears know active tuberculosis as ‘galloping consumption’⁶.

The First World War had greatly increased the number of tuberculosis victims: in 1914 the annual death rate from tuberculosis in Germany was 142 per 100,000 inhabitants. By 1918 this had increased to 230 per 100,000 inhabitants.⁷ In France in 1918 one in six deaths was due to tuberculosis.⁸ When later, in 1945, armies and rivers of refugees tramped across Europe and thousands upon thousands huddled freezing and hungry in emergency accommodation, air-raid shelters, barracks and prisoner of war camps, few had the resources to fend off infection from tubercle bacilli.

Tuberculosis mortality reached new heights, as in war-torn Berlin. From 82 deaths per 100,000 inhabitants in 1938, it rose to 316 in 1946, an increase of 385%.⁹ However, writing in early 1948, Prof. Gerhard Johannes Paul Domagk (1895−1964), head of the Bayer Institute for Experimental Pathology and Bacteriology in Wuppertal-Elberfeld and discoverer of the first sulfonamide antibiotic Prontosil, warned: ‘if we only consider tuberculosis fatalities, we fail to grasp the magnitude of the catastrophe,’ before adding stark details:

Tuberculosis: From infection to consumption

Mycobacterium tuberculosis bacteria can infect virtually any body tissue or organ. Infection generally occurs by inhalation. Small foci develop in the lungs which the body encapsulates with various immune system cells. These nodules, which are also known as tubercles, primary complexes or granulomas, may become dormant and have no ill effects. Only in some 5–10% of those infected does the disease progress to tuberculosis.

But dormant foci may reawaken many years after infection, in particular in low immunity states, due for example to old age, disease (AIDS) or medication (immunosuppressants). If the tubercle bacilli replicate in the primary foci, the foci grow in size and break into blood vessels, thereby spreading the pathogens throughout the body. The sites of predilection, after the lungs, include the meninges, lymph nodes, bone, kidney, ovary, and epididymis, all of which are instances of extrapulmonary tuberculosis. When the immune system is particularly weak, tubercle bacilli spread throughout the body via the bloodstream and settle in multiple organs creating disease foci the size of a millet seed (Latin milium). Miliary tuberculosis is generally fatal within days in the absence of effective drug therapy.

However, pulmonary tuberculosis is the commonest presentation of the disease. Patients who do not cough up bacilli are said to have closed tuberculosis. Open tuberculosis, on the other hand, is when a tuberculous focus in the lung breaks into a bronchus leading to the expulsion of active pathogens with every cough. Such a patient may infect up to ten others in one year. Early diagnosis and treatment are essential. Symptoms include coughing, weight loss, loss of appetite, tiredness, fever, night sweats, and blood-stained sputum.
Such a scenario spurred tuberculosis researchers to often untold efforts and risks in their determination to control this calamitous disease, on both sides of the Atlantic. The war may have spared America and its people may not have been starving in overcrowded emergency accommodation, yet they were still dying of tuberculosis, despite their sunshine sanitaria. Tuberculosis was the number one killer in the 15–35 year age group. In 1948 there were 43,833 tuberculosis deaths in the USA. Even in 1953 52.6 per 100,000 Americans contracted tuberculosis and 12.4 per 100,000 died from the disease.

But in addition to the crying urgency, the scientific foundations enabling the discovery of effective drugs for treating tuberculosis had been well established by the 1940s and 1950s: the pathogen, Mycobacterium tuberculosis, had been identified as far back as 1882, along with a number of its highly specific properties. In both cell culture and animal experiments there were established procedures for studying how its replication could be arrested. However, the first antibiotic against tuberculosis discovered in this period failed to live up to its early promise.

Help from below: streptomycin

We can presume that there were tubercle bacilli in the soil long before the advent of human beings. It was thus no accident that the soil was to provide the first drug treatment for tuberculosis. More exactly the drug was the product of soil-based microorganisms, bacteria that – like fungi – develop multicellular structures and hyphae. Antituberculous efficacy was discovered in a laboratory at Rutgers University, New Jersey, headed by a microbiologist whose first degree had been in agriculture: Selman Abraham Waksman (1888–1973), eminent pediatrician and early Nazi enthusiast, who joined the Party in 1923, but was later imprisoned after turning against the regime. Waksman had been commissioned by the American Tuberculosis Society to study the survivability of tubercle bacilli in soil. His coworker Chester Rhines discovered that tubercle bacilli survived very well in sterilized soil samples. They even replicated in soil samples enriched with various soil bacteria. But if the soil samples were not sterilized and nothing was done to destroy the soil fungi, tubercle bacilli counts decreased. Nevertheless, the bacilli still managed to survive in the soil for months, even if a complex microbiological population made life difficult for them. Rhines failed to identify which of the soil microorganisms might be destroying the tubercle bacilli. Initially no further experiments with tubercle bacilli followed these eye-catching data published in 1935, Waksman being more interested at the time in how soil bacteria interacted with each other. As he discovered, this interaction consisted of brutal competition for what space and nutrients were available, waged using ‘chemical weapons’.

Things changed when in 1939 at the Rockefeller Institute in New York one of Waksman’s former doctoral students, René Dubos (1901–1982), isolated these chemical weapons from a soil bacterium Bacillus brevis and used them to combat bacterial infection. These ‘antibiotics’ – Waksman coined the term in 1942 – isolated by Dubos proved too toxic for humans, whether administered intravenously or orally, but could be used topically in wound infections and on the skin. More importantly they inspired researchers’ imaginations and rekindled hope: why shouldn’t an antibiotic be found against tuberculosis and why shouldn’t it be in soil? The antibiotics that already existed, such as Fleming’s penicillin, isolated from a mould, and Prontosil, the first synthetic antibiotic, were powerless against M. tuberculosis.

From this point on, with the financial backing of the George Merck & Co drug company, Waksman’s laboratory looked for new antibiotics – above all against tuberculosis, concentrating on inhibition of the tuberculosis pathogen by soil-based microorganisms, mainly bacteria. Merck’s involvement was not only financial: while Waksman and his coworkers were busy with the microbes, Merck scientists concentrated on the chemistry and pharmacology of the resulting antibiotics. The financial contract stipulated that Merck would patent all discoveries of practical relevance and would then turn over 2.5% of related drug sale income to Rutgers University.

On October 19, 1943 one of Waksman’s doctoral students, Albert Schatz (1920–2005), isolated an antibiotic for the first time from the bacterium Streptomyces griseus. They baptized it streptomycin. In January 1944 Schatz, Elizabeth Bugie and Waksman published their discovery that streptomycin inhibited the growth of various Gram-positive and Gram-negative bacteria. Other publications followed in mid-1945 showing that streptomycin inhibited the growth of tubercle bacilli in culture and

with Degkwitz citing the following figures for Hamburg alone: 46,000 patients with open tuberculosis, and 150,000 in need of treatment, for whom only 12,000 sanitarium beds are available.\(^9\)
animal studies. The antibiotic was even tested against the most virulent human tuberculosis bacteria: H37Rv, a strain also used by subsequent Roche researchers for testing their antituberculosis drug candidates.

The first results of clinical trials of streptomycin were published in 1945 and 1946. It is fair to assume that the first tuberculosis patient to receive streptomycin was treated with material that Schatz had manufactured in labor-intensive laboratory work. But from 1946 onwards Merck took over production using biotechnology in fermenters at its plant in Elkton, Virginia.

No drugs without patents

When in 1945 the potential of streptomycin began to dawn on Waksman, and he sensed that Merck’s production capacity might not cover requirements, he approached Merck with the request that they revert the patent rights to Rutgers University. Other companies should also be able to become license holders. Merck came to an agreement with him, devolving the patent rights negotiated with Waksman in 1939 back to the Rutgers Research and Endowment Foundation. However, Merck insisted on retaining a rebate on royalties for the nonexclusive license to produce streptomycin as partial compensation for the funds it had ploughed into the drug’s development. This left the way open for other companies to acquire manufacturing licenses for the urgently required streptomycin.

At this point Waksman also persuaded his codiscoverers Schatz and Bugie ‘to forgo all revenue from the streptomycin patent in favor of the Rutgers Research and Endowment Foundation’. However, Schatz later discovered that Waksman had negotiated a contract with the Rutgers Foundation guaranteeing Waksman personally 20% of the revenue from the streptomycin patent. The generous Schatz took legal action in 1950 which secured him compensation and 3% of the annual streptomycin license royalties received by the Rutgers Foundation, but also — as it transpired — bedeviled his scientific career. Waksman’s personal share of the income was reduced to 10%, and 7% was distributed among the other laboratory coworkers involved in the discovery of streptomycin. Waksman himself later reduced his share to 5%.

As for Rutgers, it was to maintain the rule denying a company sole rights to an antibiotic, which eventually led to the university having to abandon antibiotic research.

Disillusionment

The Nobel Prize for medicine was awarded to Waksman alone in 1952 for ‘his discovery of streptomycin, the first effective antibiotic against tuberculosis’, thereby embittering Schatz and the physicians involved in the clinical trials of streptomycin.

Not only that, but streptomycin sadly failed to live up to its early promise as a wonder drug against tuberculosis. It did not work in all patients and ‘cure’ was often short-lived. If clinical tuberculosis relapsed in patients treated with streptomycin, their tubercle bacilli often proved to have become streptomycin-resistant. Worse yet, streptomycin was also ineffective in those who had acquired their infection from patients with streptomycin-resistant tuberculosis. Streptomycin damaged the auditory nerves in some patients, some of whom became deaf or hard of hearing during treatment. The situation improved somewhat when in America the first controlled clinical trials took place of combination therapy: streptomycin combined with para-amino salicylic acid (PAS).

Brilliant idea: para-amino salicylic acid

In contrast to the discovery of streptomycin, PAS was the fruit not of intensive microbiological experimentation in the laboratory but of an inspirational thought experiment. In neutral Sweden in 1940/1941 the Danish professor of physiology, Jørgen Lehmann (1895–1988), who headed the central laboratory at Sahlgrenska University Hospital, read the papers published by his colleague Frederick Bernheim (1905–believed to have died in 1988) at Duke University medical school. Bernheim reported that oxygen uptake by tubercle bacilli increased after the adding of acetylsalicylic acid (aspirin). The increase was dependent on the aspirin concentration and also occurred only after a ‘latent period’ which Bernheim postulated was required in order to ‘hydrolyze the aspirin acetyl group’. Bernheim had previously studied the influence of various substances on tubercle bacillus metabolism. He concluded that aspirin or similar compounds could be important for tubercle bacilli. Lehmann developed these thoughts further: if the acetylsalicylic acid molecule could be modified in such a way that it would still be taken up by tubercle bacilli to generate energy, but could then no longer be put to that purpose, it might perhaps prove a cure. But what kind of modification exactly? In Lehmann’s own words: ‘In fact, it was simple. In the sulfonamide there was an
Para-amino salicylic acid

amino group in the para position and if you changed the amino group for another group or put it into the ortho or meta position, then the bacteriostatic effect diminished or disappeared.23

Lehmann therefore proposed to the Swedish mid-sized company Ferrosan that they synthesize a modified aspirin incorporating an amino group in the para position on the acetyl group. The structure may have appeared supremely simple on paper (see formula), but was not simple to manufacture, at least initially. In addition it had already been synthesized early in the 20th century by German chemists and could therefore no longer be patented. A Ferrosan chemist nevertheless started work on a new synthesis and the company provided Lehmann with the substance for both his laboratory research and later also for the clinical trials.

Lehmann conceived and tested PAS not only single-handedly in the laboratory, he also tested it on himself. Only after he had swallowed and injected the substance himself did he release it for trial in a young woman with lymphoma and bone tuberculosis. In spring 1946 the press was informed of test results in other patients.24 The substance became commercially available the same year and entered wide clinical use.

PAS had neither the severe side effects of streptomycin, nor did it require injection, being active by mouth. It was also simpler to manufacture by chemical synthesis than the biotechnology used to produce streptomycin. But both drugs were merely bacteriostatic: they inhibited the growth of tubercle bacilli but could not kill them. In addition resistance developed quickly against both drugs. Combination therapy with the two drugs helped patients until the emergence of disease due to new tubercle bacilli resistant to both agents.

Toxic yet trailblazing: the thiosemicarbazones

Bayer had initially abandoned tuberculosis research with the outbreak of the Second World War. However, Domagk was then working at Bayer’s Research Institute for Experimental Pathology and Bacteriology in Wuppertal-Elberfeld. Based on his experience in and after the First World War, he feared a new tuberculosis epidemic. On November 9, 1940 in a letter to Bayer management he strongly recommended reinitiating tuberculosis research. Soon after getting back to work, Domagk discovered that sulfonamides ‘containing a thiazol caused remarkable inhibition of tubercle bacilli’.25 By November 1941 the Elberfeld scientists had realized that thiosemicarbazones had striking antituberculous effects in culture and animal studies. But in the first half of 1944, they had to abandon this line of research a second time. Relentless bombing raids reduced the town of Elberfeld to rubble. Most of Domagk’s coworkers were homeless, injured, or dead.

Many difficulties had to be overcome in order to resuscitate tuberculosis research at Bayer after the war. Only in October/November 1945 did the British occupation force allow the Elberfeld research laboratories to reopen. In the war-ravaged Germany of the time scraping materials together for research was also anything but simple: ‘In the initial postwar years’, remembered Fritz Mietzsch (1896–1958), head of research in Elberfeld in 1954, ‘we found ourselves in a situation in which it was almost impossible to obtain the animal material utterly essential for pharmaceutical research because of the food shortage. Such material was either earmarked for human nutrition or could not be produced in the first place because of the feedstuff shortage.27 The main problem, however, was recruiting new coworkers. Many members of the

26 Domagk G. Lebenserinnerungen [Memoirs (in German)]. Vol 1, p. 265; BAL.
Tibione (Conteben)

28 Prof. Bernhard Fust MD had already worked on tuberculosis as a doctoral student. In 1949 Roche made him head of its chemotherapy department, a position he held till 1967, while simultaneously lecturing at Bern University.
29 RHA: PD.3.1.RIM-102670 b N589.
32 Cost and side effects ruled out nicotinamide as a medicine for the millions, although the “pellagra vitamin” was used in rare cases in much lower doses, for example in 1952 in some of the first patients with tubercle bacilli to become resistant even to isoniazid (INH, Rimifon).
33 Yet the vitamin B studies were far from in vain: a molecular feature of nicotinamide, the pyridine ring, was to become an essential component of the first real antituberculosis drug.

Isonicotinylhydrazine (INH): an intermediate product becomes a clinical drug candidate

In the Chemotherapy Laboratories of Hoffmann-La Roche Inc. in Nutley, New Jersey German physician Robert Julius Schnitzer (1894–1987) and American bacteriologist Emanuel Grunberg (1922–1995) began tuberculosis research in 1949. They tested combinations of nicotinamide, Conteben and PAS in mice infected intravenously with H37Rv. Old workforce had been killed or scattered to the four winds by war. This also applied to the Domagk family; his mother starved to death in flight from East Prussia. His sister survived the flight and reached Wuppertal in January 1946 ‘in a pitiable state’.28 His wife and three of his children remained evacuated.

Nevertheless, progress in thiosemicarbazone research went so well that in 1946/1947 Domagk felt ready to proceed to clinical trials. One substance, p-acetylamino-benzaldehyde-thiosemicarbazone, proved especially effective and was later marketed in Europe as Conteben. In the USA it was branded as Tibione (‘TB one’). However, reports on its clinical use were ‘only published tardily and in relatively few number, as streptomycin had meanwhile become available, mostly in combination with PAS, and had become accepted as the drug of choice. Indications for the thiosemicarbazones became increasingly narrower due to their toxic side effects and relative inefficacy in certain forms of tuberculosis’.29

Small in effect against TB but large in impact: a vitamin B

Paris, 1945: Contravening Hitler’s orders, the Germans withdrew without destroying the city. At the Pasteur Institute Frenchman Vital Chorine was working on tuberculosis. He discovered that nicotinamide, a B2 complex vitamin, had a positive effect on tuberculosis in guinea pigs. The Bayer chemists seized on this information with interest. It was to influence their own syntheses of active substances somewhat later.

But the information also made experts at Roche, the leading vitamin manufacturer of the time, sit up and take notice. Not only did Roche develop the requisite laboratory research capacity for tuberculosis research, it also ran clinical trials with nicotinamide in tuberculosis patients in Switzerland and neighboring France, as well as in Portugal and Italy. However, the results were inconclusive.

Roche-Basel researchers Bernhard Fust (1910–1973) and Alfred Studer (1917–2005) confirmed Chorine’s findings in animal studies and showed that high-dose nicotinamide (2.8 g/kg body weight) was even more effective in tuberculosis than streptomycin or PAS.

But the high doses required spelled doom for nicotinamide as a potential antituberculosis drug. An internal report noted that a 60 kg human would need to take 168 g daily to match the effect in guinea pigs.31 Cost and side effects ruled out nicotinamide as a medicine for the millions, although the ‘pellagra vitamin’ was used in rare cases in much lower doses, for example in 1952 in some of the first patients with tubercle bacilli to become resistant even to isoniazid (INH, Rimifon).32
Like Domagk, Schnitzer had some rough years behind him and the two may even have met once before the war. Born in Berlin, Schnitzer studied medicine there from 1913 to 1918. In 1919, as Spanish flu raged in the city, he was Assistant at the Charité Hospital before working for nine years in the chemotherapy department at the Robert Koch Institute in Berlin. In 1928 he became head of the chemotherapy department at I.G. Farben, at the Hoechst site in Frankfurt am Main.34

Schnitzer worked on antituberculous chemotherapy at Hoechst until his dismissal as a non-Aryan on August 24, 1938. A month later, on September 30, he was removed from the medical register. He then found work in the Jewish Hospital, ‘cleaning the dishes’, as he later recounted.35 On November 12, he was deported to Buchenwald, from where he was released in January 1939 having undertaken in writing to leave Germany within four weeks. Schnitzer dispatched his children Muriel and Bertram on a Kindertransport to Belgium, while he and his wife fled to France with the ten Deutschmarks they were allowed to take with them. There the family was reunited. Schnitzer worked a few months for Rhône-Poulenc and also applied to Roche. However, the company could not get him an immediate visa. Schnitzer therefore traveled on to Canada, working in the Connaught Laboratory at Toronto University for two years. In 1941 he became head of the chemotherapy laboratory at Roche-Nutley, and in 1946 he began work, initially on sulfonamides, with the bacteriologist Grunberg, fresh from his degree course at Yale.36

Early in their tuberculosi research Schnitzer and Grunberg discovered that the combination of PAS, nicotinamide and Conteben arrested tuberculosis in mice even if PAS and nicotinamide were given in doses that were ineffective on their own. They concluded that the three substances were synergistic in their effect. Schnitzer and Grunberg also tested many new substances synthesized by the Nutley chemists based on the structure of nicotinamide and the general structural formula of the thiosemicarbazones. These also included the isonicotinylhydrazine (INH, isoniazid) first obtained by Herman Herbert Fox (born 1912?) on August 12, 1949 as an intermediate product. Fox registered it on July 7, 1950 under the internal product number Ro 2-3973 for testing for antituberculous effect.

This substance was to astonish Schnitzer and Grunberg in the summer of 1950 with its utterly remarkable activity against tubercle bacilli.37 As before, the model that they used in their studies was the mouse infected with H37Rv tubercle bacilli. In report number 7273 dated December 20, 1950 they informed Roche management:

“One compound, Ro 2-3973, appeared to be of outstanding activity. Although its toxicity was in the same range as that of the other members of this group, the activity in the tuberculous infection of mice was unusually high, twenty times higher than that of streptomycin and more than ten times higher than that of Tibione… Ro 2-3973 seems to have in addition still another unusual property. As is generally known, PAS and streptomycin exert in the mouse experiment strictly a bacteriostatic effect. As
In December 1950 the Roche-Basel laboratories also referred Ro 2-3973 'for testing for tuberculocidal activity'. There followed studies of Ro 2-3973 (INH) and Ro 2-4572 (the isopropyl derivative of INH, later baptized Marsilid) in guinea pigs and monkeys infected with tuberculosis. Tolerabilities were tested in monkeys, dogs, rats, and mice; the chronic toxicity of INH was determined over the 6-month period from December 1950 to May 1951.

Culture studies showed INH to be markedly superior to other derivatives. It was even active against H37Rv tubercle bacteria down to a dilution of 1:60 million. In comparison, the isopropyl derivative showed no inhibition of tubercle bacteria below a dilution of 1:600,000. Nevertheless, Roche synthesized other similar compounds and tested them in the laboratory. The three that were eventually tested clinically starting in June 1951 by Edward Heinrich Robitzek (1912–1984) and Irving J. Selikoff (1915–1992) at Sea View Hospital on Staten Island, a New York City tuberculosis institute, were a glucosyl derivative of INH (starting June 19, 1951), the isopropyl derivative of INH (starting October 2, 1951), and finally INH itself, for which testing only started on December 17, 1951.38

These substances were first administered only to the most serious and hopeless cases of tuberculosis, at doses of 2–4 mg, and later also 10 mg/kg body weight. All other treatments, ranging from strict bedrest, through drug therapy with streptomycin or streptomycin plus PAS (most patients), to surgical resection of the tuberculous foci up to and including pneumothorax (some patients), had been tried and tested to no avail. The patients, whose ages ranged from 10 to 70 years, with most between 20 and 39 years, were emaciated, pyrexial, weak, and anorexic, with severe coughs. Their sputum simply teemed with tubercle bacilli.

Most of these hitherto incurable patients became apyrexial after just a few days, in some cases after just 36 hours. Weight gain became apparent within weeks, with all returning to their normal weight after around 8 weeks. Many gained between 5 and 14 kg within 9 to 15 weeks of treatment. Persistent coughing was alleviated, sputum reduced, and general well-being notably improved. In some cases, tubercle bacilli became undetectable in either gastric juice or sputum. The test substances were thus capable of killing bacilli in both animals and humans, as had never been observed with either streptomycin or PAS.

When the first INH results were presented to Roche CEO Emil C. Barell (1874–1953) during a visit to the USA in 1951, he is reported to have said:

‘Gentlemen, this new Roche drug is such an important contribution to humanity that we shall have to price it in a way that even poor people all over the world can get it without difficulty. In this case, we should not worry about profits but concentrate on ensuring there is enough available for everybody who needs it.’39


30 described before by us, if the effective treatment of the usual intravenous infection is discontinued after the twenty-one day period, typical miliary tuberculosis develops after a twenty-one day period. In a similar type of experiment with Ro 2-3973 it was found that the mice intravenously infected with the standard dose of M. tuberculosis H37Rv, treated by medicated diet for 21 days with 250 mg/kg or 50 mg/kg, and then held without treatment for another three weeks period, did not develop the expected miliary tuberculosis.'
Herman Herbert Fox first synthesized isonicotinylhydrazine (INH, isoniazid) at Roche on August 12, 1949 and released it the following July for testing as a potential antituberculosis drug.

This chivalrous intention was carried out to the letter, albeit differently from how those present at the time may have envisioned. Several firms brought the drug onto the market in 1952, at a price that soon became modest, if only because of the competition involved. However Roche, Squibb and Bayer were the only companies that had researched INH in culture studies and in animals and humans.

Tuberculosis was a high-priority medical problem on both sides of the Atlantic. But so widespread had it become in postwar Germany that the Central Committee for Control of Tuberculosis in the British Zone, for example, felt impelled to draw up medical and welfare guidelines for placing patients with pulmonary tuberculosis in positions of employment.

Bayer not only pursued an intensive search for new antituberculosis drugs at its Elberfeld site, it also manufactured the ‘old’ antituberculosis drug PAS, sold as Passalon, starting in September 1949, streptomycin, starting in February 1950, and its own product Contebe, starting in 1950. Like Schnitzer and Grunberg in America, Domagk in Germany also tested combinations of existing antituberculosis drugs. He performed a wide range of studies with PAS, streptomycin and Contebe in vitro with tuberculosis bacteria on a variety of culture media and in vivo on guinea pigs infected with human tubercle bacilli and rabbits infected with bovine tuberculosis.

As already mentioned, Bayer scientists were also familiar with the nicotinamide studies. As a result, they too were soon hot on the track of the antituberculous activity of INH. Starting with thiosemicarbazones, various thiosemicarbazides and carboxylic acid hydrazides were systematically tested, with the turn of INH probably coming on March 28, 1951. Domagk himself described discovering the substance’s antituberculous activity in the Deutsche Medizinische Wochenschrift in 1952 as follows: ‘Further experimental studies yielded particularly interesting results when I was given substances by Hans Offe (Main Scientific Laboratories, Leverkusen) to be tested for tuberculostatic activity. Offe anticipated special tuberculostatic properties based on particular theories about the relationship between chemical constitution and tuberculostatic efficacy, on which we have reported elsewhere. The study of these substances proved highly rewarding because they were entirely novel substance groups in the chemotherapy of tuberculosis. We could therefore also perhaps expect that their mode of action against the tubercle bacillus would differ from that of the tuberculostatics known to

Daniel Murphy, 61, was one of those tuberculosis patients at death’s door who received experimental isoniazid. Tuberculosis bacteria had colonized his tongue which was so swollen that he could no longer eat and was almost unable to talk. On admission to the hospital, he was said to have croaked, according to Dr. Robitzek: “I don’t believe in anything anymore. The quicker it’s all over, the better”. For the first few days in hospital he was on artificial feeding. It took two weeks for him to respond to treatment with isoniazid; after one month he was able to eat again with virtually no problem and his tongue appeared normal. The photograph shows him with his nurse Effie K. Whitted and he has clearly found a new lease of life.
date. Offe and Siefken later undertook a comprehensive study of this group, including a large number of acid hydrazides, their hydrazide-hydrazone derivatives, and similarly structured cyclic compounds, totaling over 500 compounds. Some compounds in these new substance groups, in particular isonicotinic acid hydrazide (Neoteben, isoniazid) and its hydrazones, e.g. the glucose derivative and cyclic and heterocyclic oxo derivatives, gave substantially more favorable study results in some cases than PAS or even streptomycin. We found it surprising that nicotinic acid hydrazides failed to live up to our expectations in the animal studies, in contrast to the corresponding derivatives of isonicotinic acid.45

The Bayer History Archive in Leverkusen contains a letter of September 3, 1951 in which chemist Hans Albert Offe (1912–1993) writes to Domagk about INH, the Bayer product code for which was OS 711: 'The results of your in-vitro studies and some of your animal studies of isonicotinic acid hydrazide and its derivatives prompt the idea of getting Dr Hecht to run toxicology and pharmacology tests at the earliest opportunity on at least one of the derivatives... The first 3 kg of OS 711 were delivered to tableting on July 31, 1951. Further larger quantities will soon be ready to enable clinical trials to start in October.'46

Domagk then wrote on September 6, 1951 to Bayer-Leverkusen CEO Mertens:

But I consider it urgent that we at least issue a preliminary communication on OS 711 and its derivatives in the manner formulated with Prof. Bayer and Dr Offe in order to safeguard our priority and emphasize the merit of our company and our laboratories in which the pioneering work has been undertaken, before even more leaks out and is reproduced."47

A few days later in New York Domagk attended the XIIth International Congress of Pure and Applied Chemistry at which Roche chemist Fox gave three talks on synthetic tuberculostatics. The published abstract of one of these presentations even contains the structural formula of INH, although featuring only as an intermediate product along a synthetic pathway leading to a thiosemicarbazone derivative of INH.48

Why did Fox risk showing INH? Presumably because he saw no risk involved. INH was non-patentable, having been synthesized in 1911 by Hans Meyer and Josef Mally at Charles University in Prague. Its biological properties had not been further explored since.49 Perhaps, despite the unambiguous results of the laboratory microbiology tests, Fox did not yet take the non-patentable substance seriously for the cure it was to become. INH had indeed already been released for clinical trial along with two other derivatives but patentable INH derivatives took precedence in this regard. Roche laboratory INH was only tested in tuberculosis patients in December 1951.

What may Domagk have been thinking when he read the Fox abstract and came upon the formula of INH as an intermediate product in a synthesis? No thoughts are recorded in the diary he left behind. He only mentioned that at this meeting he was invited to give an impromptu 15 minute talk on antituberculosis drugs after the cancellation of a presentation by an Italian. ‘It was my
first unprepared talk in English’, he wrote in his report on the America trip.29 In his improvised talk Domagk also spoke of the antituberculous effects of thiosemicarbazones and hydrazones. He did not show the formula of INH.

On returning to Germany in early October, however, Domagk immediately arranged for OS 711 to be released for clinical trial in tuberculosis patients by Prof. Philipp Klee (1884–1978) in the Department of Medicine at Wuppertal-Elberfeld City Hospital.50

At the XIIth International Congress of Pure and Applied Chemistry in September 1951 Roche chemist Herman Herbert Fox gave the formula of isoniazid (INH) its first public airing, but only as an intermediate product along the synthetic pathway of a more complicated thiosemicarbazone structure, as shown by this extract from the volume of abstracts. By this time Roche had already released INH for testing in tuberculosis patients.

In Klee’s department the product was known as Novoteben. On February 20, 1952 Bayer renamed it Neoteben, a trade name it had previously briefly registered for another thiosemicarbazone compound that was subsequently dropped. This was a source of some confusion.

By December 1951 Domagk must have been confident of the exceptional potential of OS 711 because he wrote to the head of the main scientific laboratory at Bayer-Leverkusen, Prof. Otto Bayer, on December 4, 1951: ‘I have good grounds for ‘optimism’ and would consider it appropriate if OS 711 and OF 807 were already in large-scale manufacture, even if no clinical results are yet available apart from the fact that OS 711 itself, viewed as poorly tolerated by pharmacologists, turns out to be surprisingly well tolerated in humans. Our experimental data show that there can be absolutely no doubt either as to the superiority of its clinical effect over PAS, and it would be a pity if we were to lose too much time in clinical trials. You can only dislodge PAS and take over its world market if you can soon have so much OS 711 available that you can meet all requirements’.52,53

The Squibb Institute for Medical Research, part of the American company E.R. Squibb and Sons, also located in New Jersey (New Brunswick is but a half-hour’s drive from the former Roche research site), had also discovered the antituberculous activity of INH in 1951. The Squibb and Roche researchers in New Jersey were familiar with each other. Today, 60 years on, we can only speculate to how much this may have contributed to the near-simultaneous discovery of INH.

According to a 1978 article, 40% of Squibb Institute scientific staff at the time was involved in the search for oral antituberculosis drugs. A team of 24 researchers tested over 8000 substances. This was probably how, at Squibb too, chemist Harry L. Yale synthesized INH (SQ 7425) in the summer of 1951, again as ‘only’ an intermediate product in the six-stage synthesis of a putative antituberculosis drug, isonicotinaldehyde-thiosemicarbazone. He only released this intermediate product to his colleagues for testing because this was required by standard operating procedures.54

‘On New Year’s Eve 1951 it transpired that researchers at the American company Squibb were testing the same substance at the same time’, remembered Roche researchers years later in the house journal Roche-Nachrichten (Roche News).55

It was important to act fast. On January 15, 1952 Roche representatives met with their Squibb counterparts and thereby discovered, at the highest level, that in both companies the promising clinical candidate for an antituberculosis drug was none other than INH. Lawrence Davis Barney, Roche-Nutley CEO from 1944 to 1965, wrote to Barell on January 16, 1952:

‘While at first it may sound incredible that two companies independently would come upon this compound, further consideration makes it more plausible. The reason for this is that for the past five years Squibb have had an active tuberculosis screening laboratory and have tested over 5000 chemical entities during this period; half of these were developed in their own laboratories… We have learned further that Squibb have been working in the isonicotinic acid field since 1950.’56
In late January 1952, after some to-ing and fro-ing, the two firms agreed to go public simultaneously in announcing the astonishing curative properties of INH. The announcement was to be ‘first communicated in a leading medical journal and then discussed in detail at a public symposium of New York physicians on April 1, 1952...’. The press was to be informed the next day, April 2, 1952.

A sensational news item goes around the world

Reality diverged from this carefully prepared script: New York City hospitals head, Dr Marcus D. Kogel, was unwilling, and perhaps also unable, to wait in the face of pressure from the spectacularly successful cures and ‘pajama parties’ taking place on the tuberculosis wards. Without consulting Roche he called a special press conference on the evening of February 20, 1952 to report the antituberculous activity of Rimifon (INH), Marsilid (its isopropyl derivative), and its glucose derivative.

Roche-Nutley telegraphed Basel at 11.50 on February 21, 1951: ‘Due to Kogel indiscretion US press carrying articles on Rimifon forcing us to take relevant measures’. The same day corporate head office sent the following media release to the Swiss National News Agency (SDA):

After many years’ research Hoffmann-La Roche has succeeded in discovering a new drug against human tuberculosis. This compound, known as ‘Rimifon’, has proved more effective and better tolerated than previous drugs in large-scale studies in hospitals and sanatoria. The new drug will substantially lower treatment costs. Further studies are ongoing and the drug will be made generally accessible as soon as possible.

The same press release went out to the Roche subsidiaries in Montreal, Johannesburg, Stockholm, Vienna, Grenzach, Buenos Aires, Paris, Milan, Lisbon, Madrid and Montevideo, with a longer text to the editorial offices of medical journals, which ‘in this exceptional case was inserted as an advertisement’:

An antituberculosis drug has been discovered in joint research work by the laboratories of Hoffmann-La Roche. Among an array of pyridine compounds isonicotinic acid hydrazide, which is being brought onto the market under the name Rimifon, proved particularly effective both in the test tube and also in experimental guinea pig and mouse tuberculosis. In contrast to the antituberculosis drugs in clinical use to date, which predominantly inhibit replication by tubercle bacilli in the body, Rimifon also appears able to kill the pathogens.

Preliminary clinical trials have returned unusually positive results. Febrile patients with bilateral caseous pneumonia, positive sputum and severe asthenia, an apparently hopeless prognosis and little if any response to long courses of streptomycin and p-aminosalicylic acid, have been sustainedly apyrexial after a few days on Rimifon. Appetite increased remarkably so that body weight increased by 5 to 14 kg in the course of 9 to 15 weeks. The apathy characteristic of severe tuberculosis disappeared, coughing was alleviated, expectoration stopped after several weeks, and in some patients tubercle bacilli disappeared from sputum or gastric juice. Side effects (constipation, hyperreflexia, dizziness) were rare, transient and inconsequential.

Systematic large-scale study is ongoing. The manufacturers are ready, as far as this is possible, to deliver experimental amounts to those interested.
Meanwhile, in Nutley the telephone wires were humming: ‘The past three days have been hectic ones to put it mildly…’ Barney wrote Barell on Sunday, February 24, 1952, adding a little further on in the same letter: ‘Dr Kogel’s Wednesday night conference started a chain reaction of phone calls all night long and in fact most of the days and nights since then. Radio, press, magazine and other writers have been after us for information… This noon in New York we are meeting with the officers of the National Tuberculosis Association to explain to them that Dr Kogel acted on his own and not with our permission.’60 However, Barney was also able to see a positive side to the affair: ‘This premature publicity may result in a benefit to Roche, as follows: Tomorrow morning (Monday) Dr Sevringhaus61 is taking the two top men from the Food and Drug Administration out to the Sea View for a first-hand inspection of the clinical cases... This may speed up our application and acceptance by the F.D.A.’

A conflict over priority

Whereas the Squibb reaction to the near-simultaneous discovery of INH was one of somewhat laid-back surprise62, those at Bayer were more than astonished at the news. Bayer-Leverkusen CEO Dr Mertens spoke as follows in an interview with Northwest German radio on February 28, 1952:

‘The sensational announcement in the American press, in particular the New York Times, about the efficacy and chemical composition of the new American antituberculosis drug compels us to depart from our customary reserve. Surprisingly it now emerges that the new American drugs are chemically indistinguishable from the antituberculosis drugs that Bayer has developed in recent years. With the best will in the world we cannot determine how this duplicate discovery came about.’

This interview was not the end of the matter, as the Roche German subsidiary in Grenzach reported in mid-March to the company headquarters in Basel: ‘Bayer’s reaction to the first announcements about Rimifon from the USA is such that we must, in our view, comment on it. It would probably be most appropriate to go about this by conferring with the Bayer people in question and issuing a joint statement…

For example, an illustrated article in Quick, issue 11, March 16, states that during the 1945 occupation the occupation forces grabbed research data from safes at I.G. Farben and passed them on to ‘the American firms Squibb and Hoffmann La Roche’, providing them with the foundations for their current favorable results...

Subsequently in June 1952 the two companies agreed to publish the following joint statement in German and Swiss professional journals63:

‘After reciprocal inspection of the relevant documents the signatory companies below declare that in the course of tuberculosis research conducted entirely independently from one other they each identified isonicotinic acid hydrazide as a drug for fighting tuberculosis. Both companies independently released isonicotinic acid hydrazide for clinical trials in 1951.

F. Hoffmann-La Roche & Co., Limited company, Basel, August 8, 1952
Farbenfabriken Bayer, Leverkusen, August 8, 1952’64

Was it true that the research was conducted in full independence from one another? No, because articles had appeared in prestigious scientific journals on the antituberculous activity of nicotinamide, thiosemicarbazones, and related compounds. Just a glance at the structure of these substances suggests that chemists juggling with molecular building blocks on the basis of such structures would be bound one day to find themselves holding INH too in their hands. All three companies were conducting intensive research on antituberculosis drugs based on nicotinamide and the thiosemicarbazones. In doing so they synthesized INH along with other compounds – more as an intermediate product – and sent it for microbiological testing as an antituberculosis drug candidate. There was thus an inevitability to the simultaneity.
Meanwhile the premature and precipitate communication to the lay press brought problems for Roche not just with Bayer. It put the company under huge pressure to supply the Rimifon and Marsiliid wonder-drugs, along with dosage and tolerability data. Top priority was given to all operations that had anything to do with the testing and manufacture of Rimifon. On February 28, 1952 CEO Barell sent the following instructions to ten Basel departments in an internal memo:

There was much to do. It wasn’t just Roche subsidiaries and the world’s editorial offices that had to be kept informed, but above all tuberculosis specialists, in particular those who had yet to test the drug. With Squibb there was an agreement over which company would work with which clinical investigators, with Bayer probably not. Also, the drug still had to be approved. Last but not least it now had to be produced on a large scale.

Four different low-cost techniques existed for synthesizing INH. The availabilities of the requisite starting materials on the world market had to be reviewed. Competition for those resources was to be anticipated, at the very least from the two competitors already in the race.

As soon became clear, other companies were also competing for the starting materials. Nevertheless, it occurred to probably nobody at Roche not to bring INH and its isopropyl derivative (Marsiliid) onto the market on account of the competition to be expected. Nor is there any evidence that anyone in the company doubted their ability to produce the drug volumes required. Indeed, a media release from February 1952 states:

But it was clear to Roche management that they had to be faster than all the others if they were to show the world: INH is the Roche drug Rimifon.

In March 1952 Roche was producing INH at four different sites using three different techniques. In American Nutley INH was manufactured starting from the γ-picoline (γ-methylpyridine) in coal tar, in Basel from citric acid, and in German Grenzach and British Welwyn from pyridine. This had the advantage of not

Re. Rimifon

‘Given the utmost urgency, I would ask you to fast-track all work relating to Rimifon by all available means and also in doing so to have no qualms about from working on Saturdays or Sundays.’

‘The Hoffmann-La Roche company declares that sufficient drug quantities will be available as soon as mass production gets under way. We anticipate that this will be no later than May this year.’

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relying on a single starting material, thereby sidestepping shortages and price rises in any one of the starting materials required for synthesizing INH.

On March 5, 1952 Roche introduced INH as Rimifon onto the Swiss market. Starting March 6, 1952 Rimifon tablets were being distributed worldwide, for sale and clinical studies. By September 19, 1952 over 137 million 50 mg tablets of INH had been supplied, representing the transformation of at least 7000 kg of INH active substance. In June 1952 the Pharmacopoeia Committee in the USA gave INH the nonproprietary name isoniazid.67

The isopropyl derivative known by the Roche trade name Marsilid later received the nonproprietary name iproniazid. It came onto the market in June 1952.68 As later became apparent, Marsilid generated a remarkable brightening in patients' mood, leading to its additional use as an antidepressant being approved in 1957. Elucidation of its underlying mechanism of action paved the way to a new class of antidepressants: the monoamine oxidase inhibitors. However, Roche withdrew Marsilid on May 1, 1963 on the grounds of hepatotoxicity.69

Bayer trialed INH in German sanitoria and brought it onto the market in early March 1952 under the trade name Neoteben.

In addition to the differences already mentioned between Roche and Bayer, a third-hand rumor spread to the effect that Bayer had only begun trialing INH after its curative activity had been disclosed. What helped this rumor to develop was the fact, also already mentioned, that Bayer had originally earmarked the name for another product. Bayer was able to prove that the charges were baseless. But the affair caused considerable grief to Roche as well as to Bayer, with CEO Barell feeling compelled to put the record right and assure Bayer that Roche had not originated the rumors.

While the compound INH was not patentable in itself, Roche chemist Fox could at least apply for a use patent in the USA on March 7, 1952. It was entitled ‘Compositions for combating tuberculosis’ and was granted on May 6, 1952. ‘Compositions’ were henceforth patented that contained, in addition to INH (or its salts, such as the monohydrochloride), sterile water (for injecting INH) or tablet manufacturing excipients such as lactose, cornstarch, t alc, stearic acid or the like.70

Roche sought a use patent for INH only in the USA since Basel probably rightly assumed that such use patents were only relevant to the American market. It was agreed with Squibb that licensing fees were due neither from Roche to Squibb nor from

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68 A letter of June 26, 1952 records that ‘Marsilid has now been released for trade in the USA alongside Rimifon.’
69 RHA: PD.1.1.1.10-10123.
Squibb to Roche.\textsuperscript{71} The companies even agreed that whichever company was granted patent rights would give the other a 50% share of the accruing license fees.\textsuperscript{72} Squibb, which brought INH onto the market as Nydrazid, had also filed a type of use patent application as early as January 1952. But it was less advanced in trialing the substance in humans, which explains why the patent rights went to Roche. The agreement between the two companies was nevertheless to their mutual advantage because it might otherwise have taken years of wrangling for the patent to be granted.

In the later months of 1952, despite Roche’s American use patent, no less than five other companies in addition to Squibb and Bayer brought their versions of isoniazid onto the market. The inevitable followed: a catastrophic price collapse before the year was out. The 1 kg of INH that cost $5000 at the outset was worth barely one tenth of that by the time it was in tablet form. As an active substance INH cost only $200–300/kg. And everything pointed to a further fall in price, settling at around $18/kg for the active substance and approximately double that for INH in tablet form.\textsuperscript{73}

Were there misgivings over unprofitability? According to a Roche internal report of July 23, 1952 about a meeting between a Roche staff member and the commercial head of pharmaceutics at Bayer in Leverkusen:

‘Bayer knows that a multiplicity of companies have jumped on the manufacturing bandwagon. Only a few will stand the test of time. The more an individual company manufactures, the cheaper the price becomes. Might we not one day be interested in purchasing our substance from Leverkusen?’

Roche stuck with its own production. ‘We must be sure that in Rimifon we possess a tuberculostatic that will not only prove a most valuable complement to the few antituberculosis drugs already available, but may well in time replace them’, states with measured optimism an internal Roche report from 1952. Whoever may have written these lines was to be proved right. INH has remained to this day the number one drug in tuberculosis treatment. In the figurative phrase of a medical historian, INH spelled ‘an end to death on the Magic Mountain’ and saved the lives of millions of tuberculosis patients. It also was, and remains, cheap. In 1953 one 50 mg tablets cost 3.75 Swiss francs; an hour’s wage for a company worker at the time was 3.05 francs.\textsuperscript{74} By comparison: in 1952 treating tuberculosis with streptomycin required 1–3 g/day\textsuperscript{75} of the antibiotic at a time when 5 g streptomycin cost $2.20.\textsuperscript{76} In Switzerland, however, most tuberculosis patients at the time did not have to bear these costs themselves, paying little or even no personal contribution. This was because since January 1, 1931 the Federal Government aided the health insurance funds that offered supplementary insurance for tuberculosis. The tuberculosis insurance consisted of an income replacement insurance that paid out a daily allowance, while compulsory health insurance covered treatment, medication and part of the cure cost in an approved sanatorium.\textsuperscript{77} In 1953 over 90% of Basel residents were entitled to the benefits of tuberculosis insurance.

INH not only spelled the end of death in tuberculosis sanatoria, it heralded the end of the sanatoria themselves. Not the least of its achievements was an easing of the financial burden on health insurance funds, since sanatorium treatment cost much more than INH. For example, in 1952 the Basel Public Health Insurance Fund guaranteed its contributors treatment for up to 1080 days in a sanitarium charging 4.50 Swiss francs per day.\textsuperscript{78}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Rimifon_sales.png}
\caption{Rimifon sales}
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\begin{table}[h]
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\begin{tabular}{|c|c|c|c|c|c|c|c|}
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Sales (millions of CHF) & 12 & 10 & 16 & 18 & 20 & 18 & 12 \\
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\end{tabular}
\caption{Rimifon sales}
\end{table}

\begin{itemize}
\item \textsuperscript{71} RHA: Letter of April 6, 1952 from Dr E.C. Barell and L.D. Barney regarding licenses under prospective use patents for isonicotinyl-hydrazine, Roche/Squibb.
\item \textsuperscript{72} RHA: Letter of May 8, 1952 from L.D. Barney, Hoffmann-La Roche Nutley, to Dr Emil C. Barell.
\item \textsuperscript{73} Anonymous: The TB drug - A case for commercial chemical development. Chemonomics. 1952 (Spring):375.
\item \textsuperscript{74} I thank Bruno Halm (RHA) for this information. RHA: PO.7-102804 and MV.51-10454A.
\item \textsuperscript{75} Hiramatsu HC, Feldmann WH, Pliskin KH. Treatment of tuberculosis with streptomycin: a summary of observations on one hundred cases. JAMA 1946;132 (13):778-82.
\item \textsuperscript{76} I thank Pamela Eisele, Global Media Relations, Merck & Co., Inc., for this information.
\end{itemize}
In 1975 one year’s treatment with INH 300 mg/day cost only £2–3.79
Roche sold INH under the trade name Rimifon until the mid-1990s. In 1999 it sold the brand to a French company, Laboratoires Laphal SA.80

It never stops: bacterial resistance

Unfortunately, tubercle bacteria generally became resistant to INH too after 2–3 months, when the drug was given alone. As early as the summer of 1952 Domagk began receiving strains of bacilli sent to him at his request from all over Germany that had been isolated from patients in whom INH had become ineffective. On June 20, 1952 he received the following letter from the Hanseatic city of Hamburg:

‘At the request of your scientific representative in Hamburg, Dr Schürmann, please find enclosed a strain of tuberculosis that we obtained in our Neoteben studies and that proved resistant to 1 g Neoteben in animal experiments on Hohn agar... This strain was isolated after treatment with Neoteben 150–400 mg/day for 21 days. Unfortunately we couldn’t do a resistance test before starting treatment because we didn’t have the starting substance. For this reason we are unable to determine whether the strain already possessed this degree of resistance before exposure... The clinical course of tuberculosis in this patient showed no response despite administration of an approximate total 19 g of nicotinic acid hydrazide.81

In 1953 Bayer brought combination products of INH and streptomycin onto the market, orthomycin and orthomycin forte.82

Triple therapy with PAS, INH and streptomycin achieved a healing rate of 93% in 1952/1953 when INH was given daily for 8–10 months. By 1955 such triple therapy or two-drug combina-

Tactics and pacts

Let’s return to the 1950s: both Roche and Bayer synthesized, and patented, a number of isonicotinic acid derivatives starting in 1952. Thus on April 29, 1954 the German patent office granted Fox patent number 910298 entitled ‘Methods for manufactur-

80 I thank RHA head, Alexander Bieri, for this information.
81 BAL 316 003 082.
82 BAL, 1953 Bayer-Leverkusen company report.
85 Testing of Neoteben in culture studies.
Successors to isoniazid

Irony of history: the next-generation antituberculosis drugs were not INH derivatives. Why should they have been, given that ultimately the active substance in any INH derivative was always INH itself. Researchers at the time were at least aware of this. Roche researcher Bernhard Fust wrote in 1952:

“The condensation products of isonicotinic acid hydrazide with aldehydes are all more or less active, which is no surprise given that they completely decompose in the body to form free isonicotinic acid hydrazide.”

However, the next substance to take its place in the array of antituberculosis drugs still in use today harked back to the B vitamin nicotinamide, with which it has great affinity. Pyrazinamide (PZA), first tested in tuberculosis patients in 1952, simply has a nitrogen atom in place of a carbon in the aromatic ring of nicotinamide (see formulae).

Elucidating the mechanisms of tuberculocidal action of INH and PZA was to take decades and occupy hosts of scientists in research establishments worldwide. A 2003 paper proposed the following scenario: PZA penetrates the bacillus as a prodrug (i.e. an active substance precursor) by passive diffusion and perhaps also by active transport. There it is transformed by the enzyme nicotinamidase/pyrazinamidase (PZAase) to pyrazine acid, which rediffuses out of the bacillus. If the medium surrounding the bacillus is strongly acidic, the pyrazine acid is protonated and thereby overacidifying the cytoplasm and killing the bacillus. This mechanism works well until and unless mutations impair PZAase activity and make the bacillus become resistant to PZA; it also only works for as long as the bacillus bathes in an acid medium.90

In humans PZA works only for the first two months of therapy. It is thought that inflammation at the onset of infection ensures that the bacillus is surrounded by the acid medium required for PZA to exert its activity. So much for the mechanism of action of PZA. But how does INH work?

94 Fust B. Die Entstehungsgeschichte von Rimifon ‘Roche’ [The development history of Rimifon ‘Roche’ [in German]]. Proceedings of the 55th Congress of the German Society for Internal Medicine, 1952, otplant.
First studies on isoniazid mechanism of action

According to an internal Roche report from 1952 providing an update on experience with Rimifon: ‘All that is certain is that the tubercle bacilli stop multiplying in response to sufficient amounts of Rimifon; according to electron microscope studies, the nucleoids of the bacterial cells still divide, but protoplasmic cell division ceases. Still unknown metabolic changes in response to isoniazid lead to morphological changes and atrophy of the bacterial cell body, which ultimately succumbs to the host immune system. Whether vitamin displacement or interference with enzyme systems plays a role in this is still by no means clear.’

However, one thing was absolutely certain in 1953:

‘Isoniazid has little or no effect on other bacteria, fungi, protozoa or viral species. It may therefore be described as virtually a specific against tuberculosis.’

One person who wanted to better understand the effect of INH and iproniazid on both tuberculosis bacteria and patients worked in the Department of Biochemistry and Bacteriology of the Northwestern University Medical School (Chicago): the biochemist Ernst Albert Zeller (1907–1987). In 1952 he and his colleagues tested the effect of INH and iproniazid on bacterial and mammalian enzymes. Or to be more exact: they investigated their effect on the activities of bacterial diamine oxidase and guanine deaminase and mammalian diamine oxidase and monoamine oxidase (MAO), because all basic antibiotics and basic tuberculostatics were known at the time to inhibit the activity of bacterial diamine oxidase. Their conclusion: ‘The two new antituberculosis drugs also act on a purified diamine oxidase from pig renal cortex . . . Inhibition of rat liver mitochondrial monoamine oxidase by iproniazid is strikingly strong . . .’

Later, Zeller recalled that INH inhibited diamine oxidase as expected, but had no noteworthy effect on MAO at the same concentration. Iproniazid, on the other hand, proved a more potent MAO inhibitor than any previous compound.

Bacteria killer against depression

In the fall of 1952, Harry Salzer and Max Lurie, two psychiatrists working at Cincinnati General Hospital, began to investigate the
Around 400 BC

- Hippocrates (460–375 BC) provides the first description of pulmonary tuberculosis on a general basis, describing the physical signs of fever, night sweats, and emaciation.

Hippocrates-Louise (1711-1784)

- In the 18th century, Louise-Hippocrates, describes the physical signs of pulmonary tuberculosis and recommends dietary and hygienic measures.

- Diet and hygiene. 

- Phthisis = wasting, tuberculosis as a wasting disease, first description and definition (c. 460–c. 375 BC).

- Héloïse (1200–1279): first description of pulmonary tuberculosis

- François de le Boë Sylvius (1614–1672): publishes his treatise on pulmonary tuberculosis.

- 1679

- Hyacinthe Laënnec (1793–1864): invents the first stethoscope, describes the physical signs of pulmonary tuberculosis.

- René Théophile-Johann Lukas Schönlein (1826–1889): opens-air treatment of tuberculosis in Görbersdorf (then in the Prussian province of Brandenburg, now Germany, near Potsdam). In 1862 he opened a larger sanatorium, the Schönlein Sanatorium, which remained in operation until 1945.

- In 1854,1854, 1819

- 1819

- 1854

- The first artificial pneumothorax using a mercury manometer, designed by Hermann Brehmer (1826–1889), at the state sanatorium in Görbersdorf (then in the Prussian province of Brandenburg, now Germany, near Potsdam). In 1862 he opened a larger sanatorium, the Schönlein Sanatorium, which remained in operation until 1945.

- The physical signs of tuberculosis: fever, night sweats, and emaciation:

- 1880

- 1881

- 1882

- 1882

- 1882

- 1888

- In 1882, Robert Koch (1843–1910) discovers the bacterium responsible for tuberculosis: Mycobacterium tuberculosis

- 1889

- In 1889, Robert Koch publishes his treatise on tuberculosis.

- In 1890, Robert Koch describes the surgical treatment of tuberculosis (pneumothorax, a first artificial pneumothorax).

- 1892

- In 1892, Robert Koch discovers X-rays, which prove a diagnostic tool for the early diagnosis of tuberculosis.

- 1895

- In 1895, Röntgen develops a systematic light therapy for the treatment of tuberculosis.

- 1895

- In 1895, Niels Ryberg Finsen develops a systematic light therapy for the treatment of tuberculosis.

- 1906

- In 1906, Albert Calmette and Camille Guérin developed the Bacille Calmette-Guérin (BCG) vaccine of tubercle bacilli; which, among other things, permit the early diagnosis of pulmonary tuberculosis.

- 1944

- In 1944, Gerhard Domagk discovers streptomycin, the first antibiotic effective against tubercle bacilli: against tubercle bacilli, and almost independently, the same year, Waksman (1888–1973), co-worker of Selman Waksman (1888–1973), and another scientist, Albert Schatz (1920–2005), isolate streptomycin from the soil bacterium Streptomyces griseus.

- 1946

- In 1946, Jørgen Lehmann discovers the first antituberculous chemical agent against tubercle bacilli: para-aminosalicylic acid (PAS).

- 1950

- In 1950, Roche, Bayer, and Squibb discover the first highly effective chemical specific against tubercle bacilli: isoniazid (INH).

- 1952

- In 1952, nearly the same time and unconnectedly, researchers at three companies – Merck, Upjohn, and Squibb – discover the first highly effective chemical specific against tubercle bacilli: ethambutol.

- 1956

- In 1956, Gerhard Domagk discovers rifampicin, the first antibiotic of the thiosemicarbazones.

- 1961

- In 1961, Roche, Bayer, and Squibb discover rifampicin, the first antibiotic of the thiosemicarbazones.

- 1966

- In 1966, Albert Calmette and Camille Guérin develop the Bacille Calmette-Guérin (BCG) vaccine of tubercle bacilli.

- 1993

- In 1993, the World Health Organization (WHO) declares global tuberculosis a health emergency.

- WHO declares global Tuberculosis a health disaster.

Today

- Tuberculosis (TB) is a global health disaster with new strains of multidrug-resistant and pandrug-resistant TB spreading throughout the world.

- Cases of multidrug-resistant tuberculosis (MDR-TB) and pandrug-resistant tuberculosis (PDR-TB) are increasing.

- Every year, 10 million people fall ill with TB, and 1.5 million die of the disease.

- 2021

- Today, the number of TB cases is on the increase.

- Today, one in three people in the world is infected with TB, and one in ten will develop active TB in their lifetime.

- About 1.5 million people die from TB each year, more than any other single infectious disease.

- In 2021, the World Health Organization (WHO) declared global tuberculosis a health emergency.

- WHO declares global Tuberculosis a health disaster.

- WHO declares global Tuberculosis a health disaster.
mood-elevating effect of INH not in patients with tuberculosis, but instead those with severe, chronic depression, often of many years’ standing. They described their motivation in the opening sentence of their report: ‘New and more effective means of chemotherapy for mental disorders are constantly being sought by psychiatrists.’ They sensed that the euphoric activity reported as a side effect of the new antituberculosis drug went somewhat beyond the joy to be expected when patients recover from a disease considered incurable.

Some of their depressed patients had previously been treated unsuccessfully with ‘chemical agents’ against depression. At the time these included amphetamine, barbiturates, other sedatives, vitamins and subcoma insulin therapy. A good third of the patients had also previously had to endure several (up to 19) sessions of electroconvulsive therapy (ECT), which is often effective in severe depression – albeit only for a limited time. These patients were now given 50 mg INH three times daily, since no side effects were expected at this dose. Severe cases received 100 mg three times daily. Of the 41 patients they treated, the two psychiatrists relieved 28 of their depression, generally within six months. Insomnia, anorexia and listlessness all resolved. ‘But the exact ‘modus operandi’ still needs to be shown,’ they observed in 1954.

However, Lurie and Salzer had probably overlooked the fact that the results of the first Roche clinical studies of INH and its derivatives in tuberculosis patients had been conducted mainly with iproniazid. This drug had been administered to 87 of the 97 patients. Also it was not initially noticed that the studies with INH alone did not produce the same euphoric effect. Then in late 1952, orthopedic surgeon David M. Bosworth, who was testing both drugs for the treatment of bone tuberculosis, pointed out that iproniazid ‘has a marked effect on tissues aside from its bacteriostatic control of the M. tuberculosis.’

‘From then on the two products developed in different directions in their clinical use,’ reported a Roche advertising brochure that appeared in the late 1950s. While INH – still used today as an antituberculosis drug – was (unfortunately) not further investigated or utilized as an antidepressant, iproniazid carved out a career for a few years as the first real antidepressant. Perhaps this was because INH enjoyed no patent protection, but perhaps also because iproniazid caused more frequent and severe ‘neuropsychiatric side effects’ in tuberculosis patients than INH. It was not least these psychosis-producing side effects that...

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62 Among the most conspicuous side effects physicians at the time described orthostatic hypotension, muscle fibrillation, rigidity, sweating, constipation, disturbances of micturition, bradycardia and drowsiness. See Viollier, G, Quiring E, Staub H. Einfluss von oral verabreichtem Isonikotinsäurehydrazid und dessen isopropylhydrazid auf den Enzymhaushalt der weissen Ratte [Effect of orally administered isonicotinic acid hydrazide and its isopropyl derivative on the enzyme balance of the white rat (in German)]. Helv Chim Acta. 1953;36(3):724-30.
63 Salzer HM, Lurie ML. Depressive states treated with isonicotinyl hydrazide (isoniazid); a follow-up study. Ohio Med. 1955 May;51(5):437-41.
spelled the end for iproniazid as a treatment of tuberculosis. But this had shown the psychiatrists that it also acted in the brain, where it ‘could release mechanisms in the central nervous system which might lead to correction or aberration of mental processes.’

Iproniazid acted as what the experts then called a ‘psychic energizer’ in patients with depression. It produced feelings of well-being, increased appetite very substantially, gave energy and reduced the need for sleep. A typical statement of patients at the time was ‘I have not felt so good in many years.’

Then in 1956 researchers, including the Swiss Alfred Pletscher (1916–2006), later a Roche Head of Research, discovered that iproniazid raises serotonin and noradrenaline levels in the brain. Both compounds act as neurotransmitters, are biogenic amines and are metabolized by MAO. Because of its mood-lifting effect, serotonin is also known as the ‘happy hormone’.

A year later, in 1957, Nathan S. Kline (1916–1983) and his coworkers postulated that this antidepressant activity of iproniazid was probably due to the MAO inhibition found by Zeller. This was confirmed by further experiments with other MAO inhibitors, which were similarly effective in depression; some had been synthesized at Roche.

In March 1955 the FDA had licensed Marsilid for the treatment of tuberculosis in doses of 2–4 mg/kg body weight. In March 1957 it was also licensed for the treatment of depression, albeit at lower doses of up to 150 mg/day. The package leaflet contained the warning: ‘This is a potent drug that must only be used under medical supervision.’

An antidepressant drug as a novel antidepressant: for the editors of major US newspapers like the Wall Street Journal, New York Times and New York Herald Tribune in early April 1957, this was worth visiting and reporting on a Roche press conference. It was probably due not least to the fact that it was New York physicians who were not only testing the substance in patients with depression, but identifying an association between the antidepressant effect and MAO inhibition. Kline’s New York research team had reported the association on April 6, 1957 at a psychiatry meeting in Syracuse, New York. However, these articles in the US press were mainly confined to the back pages.

In Switzerland in 1957, clinical trials of Marsilid were still in progress for the new indication. But by May 27, 1958 the scene was set in Switzerland too. The Swiss Intercantonal Office for the Control of Medicines (IOCM) in Bern approved the new use recommendations for Marsilid for the treatment of depressive mood disorders. In addition to constituting a tremendous therapeutic advance, as evidenced by the fact that over a half-million patients have been treated with these compounds since their introduction only one and one-half years ago, we believe that the breakthrough in respect to understanding the biochemistry of mental illness is of even greater significance,’ wrote Kline and his co-authors with some pride in 1959.

Isoniazid: so simple a molecule, so complex an effect

There is probably nothing more complex than the human brain. It thus seems a little paradoxical that it took only five years to elucidate the mechanism of antidepressant action of an INH derivative in the brain, but over 50 years to elucidate the causes of INH’s antituberculous effect. It is also somewhat tragic that none of the protagonists involved in the discovery of INH were destined to learn why INH is ultimately able to kill tuberculosis bacteria.

In the end, in fact, the lethal effect of INH on tuberculosis bacteria again involves inhibition of an enzyme. However – and this makes things a bit more complicated and requires the use of gene technology-based investigation methods to elucidate the mechanism of action – it is not INH itself that acts as an enzyme inhibitor, but a so-called adduct produced from INH in the tuberculosis bacteria.

As early as 1953 the American microbiologist Gardner Middlebrook (1915–1986) had discovered that INH-resistant tuberculosis bacteria showed little or no catalase activity. Catalases are enzymes that convert the cytotoxic metabolic by-product hydrogen peroxide to oxygen and water. Incidentally, like many other tuberculosis researchers, Middlebrook had a special reason for his scientific work in tuberculosis: he had himself suffered from pulmonary tuberculosis.

Catalase activity thus played a role. But exactly what role? In the year 1960 Frank Winder had postulated that INH gives rise to the free radicals required for its bactericidal effect. In 1970 it was discovered that INH inhibits the synthesis of cell wall components vital to tuberculosis bacteria. These are long-chain fatty acids known as mycolic acids. Biochemical studies then confirmed that INH is actually an inactive precursor that only once inside the tuberculosis bacteria is converted by a catalase.
An antituberculosis drug as a novel antidepressant: for the editors of major US newspapers this was worth reporting on in early April 1957.

New York Herald Tribune
April 7, 1957

Wall Street Journal
April 8, 1957

to an isonicotinyl radical, which then probably inhibits mycolic fatty acid synthesis, thereby causing cell death.

By 1987 the tools were available to selectively alter the genetic material of tuberculosis bacteria. Manipulation of the genetic blueprints for individual enzymes identified the enzymes that had to be active for INH to exert its effect. These were, as discovered in the 1990s, the catalase-peroxidase enzyme KatG and NADH-dependent enoyl-ACP (acyl carrier protein) reductase InhA, which is involved in mycolic acid biosynthesis.

In 1998 it then emerged that the INH radical does not bind directly to InhA, but must first form a covalent bond with nicotinamide adenine dinucleotide (NAD). NAD is a coenzyme involved in numerous metabolic reactions.

What a mechanism of action! A small molecule penetrates the characteristic mycobacterial waxy cell wall of tuberculosis bacteria by passive diffusion to become a radical inside the bacteria under the effect of the KatG enzyme, forms an adduct with another (co) enzyme, NAD, and thereby inhibits a third enzyme, InhA, which synthesizes components of the tuberculosis bacteria’s unique membrane. Inhibition of mycolic acid synthesis spells cell death.

If all goes well, researchers will now be able to elucidate such mechanisms of drug action. However, even today, it is virtually impossible to systematically design drugs from scratch with such three-stage mechanisms of action rather than find them by screening compounds for antibacterial effect in pathogen cultures and infected cells.

Genetic methods have elucidated some mechanisms of INH resistance. One, for example, involves tuberculosis bacteria producing more InhA enzyme. A mutation in the regulatory sequence of the gene carrying the blueprint for the InhA enzyme means that inhA mRNA is formed twenty times faster.115 mRNA transports the protein blueprint out of the nucleus to the protein factories of the cell. For bacteria capable of upregulating the production of enzyme in this way, inhibiting that enzyme can’t do them much harm, because even if the resistance mechanism is known, side effects generally preclude increasing the dose of a drug to that extent.

The antituberculous activity of INH continues to occupy researchers, particularly of course because they want to better understand how resistance develops and find targets for new antituberculosis drugs. Additional mechanisms of action for INH have been postulated, but 2010 saw the publication of a paper that cast doubt on a mechanism previously thought likely.116

114 Roche employee Jörg Benz used PyMol Molecular Graphic System software to create this illustration with InhA in ribbon presentation based on the 1ZID data. NADH is the abbreviation for NAD in reduced form.


Tuberculosis today: a still-feared infectious disease

According to the World Health Organization (WHO), two billion people today are infected with tuberculosis bacteria — a third of the world’s population. In 2010 8.8 million people became newly infected, about 1.4 million died of tuberculosis and 5.7 million received treatment for it. The vast majority of the latter swallowed INH as part of their drug cocktail. ‘For people with tuberculosis that is still treatable with drugs, taking INH is often a life-saving measure,’\textsuperscript{117} is the verdict of Christine F. Sizemore, Chief of the Tuberculosis, Leprosy and other Mycobacterial Diseases Section within the Division of Microbiology and Infectious Diseases at the National Institute of Allergy and Infectious Diseases.\textsuperscript{118}

Affluent western countries such as Switzerland, with only 500 new cases of tuberculosis a year, are scarcely aware of the challenge this disease poses to humanity. But in fact, tuberculosis is still one of the deadliest and rightly most feared infectious diseases affecting mankind. As in the past, it spreads when poverty and overcrowding promote the rise of communicable diseases. In addition to this, the immunodeficiency disease AIDS has been contributing to a resurgence of tuberculosis since the 1980s. From 1985 to 1991 tuberculosis increased by 12% in the USA and by 30% in Europe. But in those regions of Africa where tuberculosis and HIV infection often occurred together, the number of patients increased by 300%.\textsuperscript{119}

Example India: isoniazid for prophylaxis and treatment

India is one of the countries most severely affected by tuberculosis. Each year on the subcontinent 1.98 million people become newly infected with tuberculosis. In 2010 the disease claimed about 320,000 Indian lives.\textsuperscript{120} Tuberculosis is the commonest infectious disease in this emerging economy with 1.21 billion inhabitants and has reached epidemic proportions. The large number of tuberculosis cases there is undoubtedly due not least to the high population density and severe poverty of broad segments of the population.

But an additional reason is that it often takes too long to make a firm diagnosis. So a person with open tuberculosis in India may infect up to 15 other people.

‘India is a country that doesn’t reimburse the cost of treating disease. Exceptions are the government’s national health care programmes or those for government employees and a small number of people who have insurance up to a certain limit,’ explains Girish Telang, General Manager of Roche Products in India. ‘Fighting tuberculosis is part of such a national programme, but the diagnostic and therapeutic protocols differs in private and governmental practice. Public institutions diagnose tuberculosis on the basis of clinical symptoms and routine investigations such as chest X-ray, sputum examination and tests for inflammatory markers. By contrast, the private sector augments these basic investigations, if necessary, with imaging techniques such as magnetic resonance imaging (MRI), positron emission tomography (PET) and computed tomography (CT). It may also use in-vitro diagnostics based on the polymerase chain reaction (PCR) to identify the genetic material of tuberculosis bacteria, if the patient requests this and can pay for it. Tuberculosis treatment is paid for as part of the government’s national programme and includes not only the drugs, but also investigations for the management of tuberculosis in public health care facilities. By contrast, patients treated in private hospitals and institutions have to bear the costs themselves for all investigations and drugs required in treating tuberculosis.’

Dr Ashok Mahashur, chest physician at P.D. Hinduja National Hospital & Medical Research Center, is convinced that ‘probably every Indian has a primary complex in his lung or adjacent

\textsuperscript{118} NIAID is a component of the National Institute of Health, which is part of the U.S. Department of Health and Human Services.
Spotting tuberculous foci: 
Help from positron emission tomography


Since 2008 the diagnostic options available in tuberculosis have included positron emission tomography (PET). This is an imaging procedure using a radiolabeled compound and is normally combined with computed tomography (PET/CT). As in cancer diagnostics, PET scans in tuberculosis also involve the use of a sugar (glucose) labeled with radioactive fluorine, fluoro-18-deoxyglucose (18-FDG). Both inflammatory and malignant cells have high glucose uptake. As a result 18-FDG accumulates in tumors, but also in inflammatory and tuberculous foci. PET cannot at present distinguish reliably between cancerous and tuberculous lesions, but this technique, which examines the whole body, helps to detect disease foci which may often be hidden throughout the body in either cancer or tuberculosis. A biopsy, in other words a sample of material taken from one of the most active foci detected, then confirms the diagnosis. ‘Once an infection (like tuberculosis) or a malignant tumor has been diagnosed, and treatment started, then PET/CT and 18-FDG scanning are well suited to treatment follow-up because metabolic changes show the response better than anatomical changes. Sometimes the lesions don’t change in size, but metabolic activity declines considerably because the active diseased cells have died,’ explains Dr Ujwal Bhure, a PET specialist from Mumbai, adding that ‘inflammatory and infectious foci are highly likely to show decreased 18-FDG uptake on PET scans performed 60 to 90 minutes after injection of the radiotracer, whereas more and more 18-FDG accumulates over time in cancer cells.’ Image intensities after a prolonged period are thus sufficient to provide a first clue. The active foci detected here by PET in the neck and chest are compatible with lymphoma or tuberculosis. Biopsy revealed tuberculosis. The patient received drug treatment and survived. The intense signal (darkening) in the brain is due neither to cancer nor tuberculosis but to the physiological fact that the brain has very high glucose uptake.
serious autoimmune disease such as lupus erythematosus or rheumatoid arthritis.

Indian epidemiologist and tuberculosis researcher Madhukar Pai, Associate Professor at McGill University, Montreal, characterizes the unholy alliance of the immunodeficiency disease AIDS and tuberculosis thus: 'HIV patients testing positive for tuberculosis have a 10-fold increased risk of developing clinical tuberculosis.' For that reason the WHO recommends at least six months of tuberculosis prophylaxis with 300 mg INH daily for HIV-infected adolescents and adults. According to a WHO report, a worldwide total of 80,000 HIV patients received INH prophylaxis in 2009.

In India an estimated 2.3 million people are infected with HIV. Do all receive INH prophylaxis? 'No,' says Prof. Alaka Deshpande, director of the Centre of Excellence in HIV Care at Grant Medical College & Sir JJ Group Government Hospital. This hospital mainly caters to the middle and lower socioeconomic group where the patients are given free medical services.

And she adds: 'There are no controlled studies. Secondly, INH resistance is rising in the general population; therefore doctors prefer to treat TB as and when it develops. It takes about eight to ten years for an HIV-infected person to reach the stage of AIDS. During these years, an HIV-infected person experiences at least two to three episodes of tuberculosis. In the early stages, when his CD4 count is robust, he develops pulmonary tuberculosis, then as
the immunodeficiency progresses, he develops extrapulmonary or disseminated tuberculosis. As per the revised National Tuberculosis Control Programme, TB cases are given DOTS, i.e. directly observed treatment, short-course. As per WHO guidelines, the patients are categorized and therapy is given. A newly diagnosed case gets category 1, which consists of INH, rifampicin, ethambutol, and pyrazinamide for 2 months followed by therapy with INH and rifampicin for 4 months. If the patient has a relapse, or if sputum does not convert into smear-negative status after two months of treatment, we add intramuscular streptomycin. However, Prof. Deshpande also uses INH prophylactically in selected cases: If a mother with tuberculosis is treated, her breastfed infant also receives prophylactic INH for six months. Patients with connective tissue receiving long-term steroid therapy are also protected with INH prophylaxis.

As Prof. Deshpande reports, rifampicin often promotes INH-induced hepatitis. Patients developing such drug-induced jaundice suspend their antituberculous medication until the jaundice subsides. Only then is it gradually restarted: first with INH and ethambutol, after a week with rifampicin, and then with pyrazinamide. Surprisingly, jaundice does not then return.

In Prof. Deshpande’s hospital, low-income tuberculosis patients receive INH free of charge. Indians who have to pay for their own medication spend about 100 rupees on a hundred 300 mg tablets of INH; this corresponds to roughly $2, or the daily wage of an unskilled worker. However, to this must be added the cost of medical consultations, which can range from between 25 and 100 rupees a visit for the general practitioner to between 500 and 3000 rupees for a lung specialist, as we learn from Anil Kukreja, Director Medical Affairs at Roche Products in India.

Tuberculosis was and is a disease of poverty. But airborne bacterial infectious diseases do not stop at palace doors.

‘We have to keep in mind that TB is an airborne disease. For example, whenever you take a taxi in Mumbai, the Indian hotspot of multidrug-resistant tuberculosis, and the driver coughs, you never know whether he has a cold or tuberculosis. The air conditioning system blows the driver’s germs into the rear seats. The same is true in the crowded buses crossing the country. Evidence shows that you can get infected if you travel for long hours close to a person with active tuberculosis who coughs. Tuberculosis is and should remain the responsibility of all of us because tuberculosis is about the air we breathe,’ warns Lucica Ditiu, Executive Secretary of the Stop TB Partnership, founded in 2001.

To borrow the words of Anjali Nayyar, senior vice-president at Global Health Strategies, New Delhi:

‘Something has to be done in India. It is urgent.’

‘We need new drugs and rapid diagnostic tests, not antibody tests or PCR-based tests,’ says Dr Hemant P. Thacker, consulting physician & cardiometabolic specialist at Bhatia Hospital in Mumbai, a middle-class hospital. He sees 20 to 30 patients a day, five to seven of them have tuberculosis.

What is needed is indeed a cheap and rapid point-of-care test for tuberculosis. Such a test should be developed in India, said the experts attending the TB Diagnostics in India: From Importation and Imitation to Innovation meeting held in Bangalore on August 25–26, 2011. ‘We are barely detecting 60% of cases, so undiagnosed tuberculosis continues to fuel transmission.
Misdiagnosis is another concern – there are dozens of inaccurate blood tests for active tuberculosis,’ according to Madhukar Pai, who also co-chairs the Stop TB Partnership’s new Diagnostics Working Group.

So more accurate rapid diagnostic tools are needed, especially those for detecting drug-resistant disease. ‘As a world leader in in-vitro diagnostics, Roche has the tools, in the shape of Roche Applied Science, to make genome-wide analyses of different new drug-resistant strains of *M. tuberculosis*, and could therefore support research in finding the specific gene sequences in tuberculosis bacteria that are responsible for drug resistance,’ commented Bhuwnesh Agrawal, general manager of Roche Diagnostics in India from 2007 until 2012.

**Going forward**

Given the large number of people infected with *M. tuberculosis*, and the pathogen’s habit of lying dormant for decades in the animal and human body at sites that immune cells often fail to locate, it seems doubtful tuberculosis can ever be eradicated – a goal that was still euphorically considered possible, and indeed vigorously pursued, in the 20th century. Tuberculosis, if untreated, can even now lead to death within five years.

From 1995 to 2009 a total of 41 million tuberculosis patients worldwide were treated with INH in DOTS programs, and six million lives saved, of which two million were women and children.122 INH, developed 60 years ago, is thus still a lifesaver for millions of tuberculosis patients.

In 2009 an estimated 250,000 tuberculosis patients worldwide had multidrug-resistant tuberculosis, meaning that they failed to respond to at least the current two most potent antituberculous agents, INH and rifampicin. Only 12% were actually diagnosed.123 And cases of extensively drug-resistant tuberculosis (XDR-TB), in which three or more second-line antituberculous drugs also fail, are on the increase.124 ‘Nobody in Europe is 100 percent protected from drug-resistant tuberculosis,’ said a medical officer at the WHO. In September 2011 the WHO therefore launched a new plan for fighting tuberculosis in Europe. The target: to diagnose 85% of all patients and treat at least 75% of them by the end of 2015. At present only 32% of patients with drug-resistant tuberculosis in western Europe are diagnosed and many stop their treatment early, which encourages the development of resistant organisms.125

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122 WHO report 2010 Global Tuberculosis Control.
123 WHO report 2010 Global Tuberculosis Control.
Acknowledgements

Unfortunately, none of the protagonists involved in the discovery of isoniazid (INH) is still alive today, 60 years later. I am therefore all the more grateful to everyone who helped me track down evidence from the past: first and foremost to Alexander Bieri and his colleagues Bruno Halm and Dr Lionel Löw at the Roche Historical Collection and Archive, but also to the staff of the Bayer Corporate History & Archives, especially Hans Herrmann Pogarell. My thanks also go to the staff of the Roche Scientific Information Service, especially Reinhard Bassermann and Carola Lefrank in Basel, who helped me get hold of the sources found in databases and the literature, and Sandra Digiacomo in Nutley, who ‘dug out’ the quoted internal research reports by Herman Herbert Fox, Robert Julius Schnitzer and Emanuel Grunberg.

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Bactrim

by Christoph Mörgeli

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Cotrimoxazole, the drug developed, produced and marketed since 1969 as Bactrim by F. Hoffmann-La Roche Ltd and Septrin by Burroughs Wellcome & Co., is one of the most effective and widely used treatments in the history of medicine. Combining two antibiotic agents, sulfamethoxazole and trimethoprim, in a 5:1 ratio, it has proven a global success in the fight against infectious disease. The drug’s mutually potentiating active ingredients act simultaneously but in different ways on bacterial metabolism and exert an astonishingly potent bactericidal effect. Bactrim simultaneously blocks two enzymes in the same microbial reaction pathway. This results in the inhibition of purine synthesis and of thymidine, thus preventing the production of bacterial deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). What was striking about this (at the time) novel dual action was that – in animal experiments and clinically – it was synergistic, not merely additive. The drug’s active ingredients also have similar half-lives, enabling them both to be administered mornings and evenings, at the same convenient 12-hour intervals. In addition, adverse effects have proved to be minor, and patients with bacterial infections can almost always take cotrimoxazole in tablet form.

Almost two billion people treated
Launched by Roche in 1969, Bactrim was added to the list of essential medicines published by the World Health Organization (WHO) in 1977. By 31 March 2011 1.884 billion people (including repeat courses) had been treated with the drug for infections of the upper and lower respiratory tract, kidneys and urinary tract, reproductive organs and gastrointestinal tract. It had cured – or in the majority of cases at least produced a significant improvement – in nearly two billion patients.

The fact that a third of the world’s population still die of infectious diseases shows how vital anti-infective agents continue to be.

Following market launch, Bactrim became a major product for Roche. While only a moderate commercial success (sales through 2011 totalled not quite 10 billion Swiss francs), its contribution to human health make Bactrim one of the truly great medicines. Doctors have used it to save more lives over the past forty years or so than all the lives claimed by war in human history (see Foreword).

Dividing total Bactrim sales by the number of courses sold works out to an average cost of about 5 Swiss francs per treatment course – a modest price considering the many hundreds of millions of human lives saved.
Even if we no longer share the therapeutic optimism of the 1970s and 1980s about eradicating infectious disease, Bactrim continues to stand out as a milestone in their management.

The co-development, co-production and co-marketing of Bactrim/Seprin offer a textbook example of successful partnering. Notwithstanding some friction and minor disputes along the way, collaboration between Roche and the British pharmaceutical company Burroughs Wellcome went well thanks to an alignment of interests and structures and some aggressively negotiated but ultimately fair agreements.

Latecomer to chemotherapy

Roche was a relative latecomer to antibacterial chemotherapy. Still, the company’s Basel and Nutley/New Jersey sites did manage to develop an impressive number of major antibacterial products after the Second World War. The sulphonamide class of synthetic antibacterials was invented by others, however. In 1935 the German pathologist and bacteriologist Gerhard Domagk discovered the bacteriotoxic effect of Prontosil rubrum, a sulphonamide dye.

Domagk was a researcher at Bayer AG, part of the I.G. Farben group in Wuppertal-Elberfeld.

Work on natural antibiotics – antibacterial metabolites produced by fungi and bacteria – had begun back in 1929 with the discovery of penicillin by the Scottish bacteriologist Alexander Fleming in London. Great Britain, the United States and their Allies introduced this significant antibacterial agent towards the end of the Second World War, at a time when Roche had little opportunity for research in this field. At the request of the US government, however, Roche did produce large quantities of penicillin at its Nutley site from 1943 onwards, alongside a flourishing vitamins operation. After 1945 the market quickly became saturated, and Roche consequently halted virtually all penicillin production in the US. Only the oral product PerOs-Cillin remained in production for a while longer.

Despite these disappointments, Roche worked intensively on anti-infectives, focusing in Nutley on fermentation products and in Basel on the chemical synthesis of antibiotic compounds. Roche Basel sold the rights to an industrial-scale process, developed under the direction of Hans Spiegelberg, for synthesising the bacteriotoxic effect of Prontosil rubrum, a sulfonamide dye.9 Domagk was a researcher at Bayer AG, part of the I.G. Farben group in Wuppertal-Elberfeld.

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Progress in sulphonamide research was also slow at Roche for the first few years. Contrary to the hopes entertained in Basel and Nutley, a superior successor to Domagk’s Prontosil was not soon forthcoming. In 1949 the company became a significant player in the sulphonamide market when it launched Gantrisin. Back in 1944 in Nutley, the German émigré chemist Max Hoffer and Heinz Moritz Wüest had succeeded in synthesising the novel drug’s active ingredient, sulfisoxazole.14 Gantrisin was a milestone in chemotherapy, and even today – despite the development of resistance – its good tolerability profile ensures continuing use in paediatric medicine and in urinary tract infections.
In 1952, Roche launched Rimifon, the isonicotinic acid hydrazide synthesised by H. Herbert Fox and identified by Emanuel Grunberg and Robert J. Schnitzer as an antituberculosis agent – at the time a milestone in the global fight against tuberculosis. This was followed in 1956 by D-cycloserine, another antibiotic directed against the still rampant tuberculosis, co-developed with researchers from other companies. Because of its toxicity, however, D-cycloserine is used only as second-line therapy in the event of resistance to other antibiotics.

Research on Gantrisin, and on sulfonamides in general, continued at Roche in the 1950s and resulted in the discovery of the isomer known as Iso-Gantrisin, followed in 1956 by Azo-Gantrisin. Based on studies by the Innsbruck chemistry professor Hermann Bretschneider, in 1959 Roche launched sulfadimethoxine (Madribon), which combined broad-spectrum activity, good tolerability and a long duration of action, particularly in pediatric medicine. The name 'Madribon', incidentally, derived from an earlier vitamin preparation that had been dropped. While systematically testing all the isomers of Madribon, Bretschneider also found the long-acting sulfadoxine (Fanasil) for use in tropical medicine, which remained effective for a week following ingestion of a single tablet.

Gantanol – developed in Japan

Gantanol, a sulfonamide launched in 1962 that would later play a prominent role in the development of Bactrim, was not initially the result of Roche research. Instead, no doubt as a result of rational planning and a bit of luck, the company had purchased the active substance sulfamethoxazole from the Japanese pharmaceutical company Shionogi & Co., Ltd. Sulfamethoxazole (Sinomin) had been developed in Shionogi’s laboratories in Osaka in 1958. Sinomin/Gantanol was a modification of Gantrisin (the nor-iso analogue) with an intermediate duration of action (four tablets daily). Gantanol was used with considerable success in urinary tract infections and lung diseases. The successor product, 'Uro Gantanol', acted even more specifically in the lower abdomen.
The last Roche advance for a long time in antibacterial chemotherapy came in 1968 with the combination product Bactrim, developed jointly with Burroughs Wellcome. This broad-spectrum therapeutic agent was to prove one of the most important products in Roche’s pharma portfolio in the 1970s and 1980s. Other products provided the wherewithal for its discovery. The tranquillisers Librium (1960) and Valium (1963) had achieved spectacular medical and commercial success. Synthesised by the Nutley-based chemist Leo Sternbach, another refugee from Nazism, they were Roche’s flagship products in the first half of the 1960s. Thanks to these two benzodiazepines, considerably more funds flowed into the company’s coffers than from the synthetic vitamins launched in 1933. While sales in 1946 were still only 221 million Swiss francs, by 1965 the total had climbed to over two billion francs, fuelled by strong demand for Roche’s new products, but also by the general economic upturn and expanded health insurance in the West. The financial opportunities this offered the company resulted, particularly in Basel and Nutley, in extensive building activity, diversification, and above all in a dramatic increase in research funding. Since 1956, the whole research organisation had been coordinated by the Roche Research Management Group (RRMG) which in 1967 had a budget of 134 million Swiss francs. Various project groups brought together the representatives of individual research teams to work on specific assignments. As medical research director in Basel, the physician Professor Alfred Pletscher also oversaw the work being done at the Group’s US and UK subsidiaries in Nutley and Welwyn. Pletscher allowed his staff a long rein but had visions for the future every bit as ambitious as those of Roche’s new Chairman and CEO, Adolf Walter Jann, a lawyer and the son of a doctor from Uri.

Tougher testing requirements

Roche Basel’s Department of Experimental Medicine was divided into pharmacology, biochemistry, chemotherapy, pathology, physiology, hematology and the experimental animal farm at Füllinsdorf. The Clinical Drug Trials Department which worked together with hospitals and university departments throughout the world also assumed increasing importance. The horrific malformations of newborn infants caused by the unconsidered use of

Leaflet for doctors on Uro-Gantanol (1960s).

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86

Meeting in the 1960s. Facing the camera, from left to right: O. Isler, A. Pletscher, O. Schneider, H. Spiegelberg, M. Montavon, E. Böhni.

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the hypnotic and sedative agent Contergan (thalidomide) from the German company Grünenthal GmbH produced shockwaves in society and from 1961 onwards resulted in significantly tougher regulatory requirements. The US Food and Drug Administration (FDA) in particular, on instructions from Congress, issued tighter licensing requirements for new medications and claimed the authority to approve clinical trials. The FDA redefined scientific procedures and staff qualifications, and demanded toxicological studies as well as studies of how medicinal products were altered or broken down in the body. These requirements were to exert a profound influence on the development of Bactrim right up to market launch.

While recognising the need for stringent approval procedures, Roche CEO Jann was outspokenly critical of what he saw as excessive clinical testing requirements and nonsensical regulatory hurdles, which he suspected were being abused for protectionist purposes. Countless trials and tests had to be repeated in each national jurisdiction, necessitating enormous amounts of paperwork, squandering research resources, making medicines more expensive and driving smaller firms to the wall.

In 1970 Roche employed about 3500 people worldwide in research. At the time 300 scientists were working in the research department in Basel, each with an average of three staff, for a total of about 1200 people. Five thousand new compounds were synthesised annually, only about 30 of which ever entered clinical trials, and the company considered itself fortunate if it managed to bring two of them to market. As research director Pletscher remarked at the company’s 1970 Chemistry Meeting:

‘Successful drugs are as rare as flawless pearls. I am convinced that individualism has a greater chance of finding such precious pearls than uniformity.’

Biology takes the lead

The early development of Bactrim played out against the background of a gradual move from chemistry to biology as the lead science in pharmaceutical research. Unlike chemists, many young bioscientists were sceptical, if not downright dismissive, about working in industry. To help bridge the divide between basic and industrial research, Roche founded the Roche Institute of Molecular Biology (RIMB) in the United States (Nutley, NJ) in 1967, and shortly afterwards the Basel Institute for Immunology.
Valium and Librium accounted for a distressingly high 62% of total pharmaceutical sales. In the Sales Department’s view Roche had ‘too many eggs in one basket’. The patents on Roche’s top-selling drugs were all due to expire within the next ten years, making it imperative to bring some profitable successors to market. This was all the more important as the side effects and addictive potential of tranquillisers were becoming a subject of heated debate.

(BII) in Basel. It’s important to remember, too, that in the 1960s pharmaceutical companies everywhere, including Roche, were experiencing a bit of a slump, following an innovative surge that yielded a number of new medicines in the 1950s. Roche’s managers were genuinely concerned about not being able to bring enough novel chemical entities to market. And they found it equally disquieting that thousands of compounds now had to be tested to find a single suitable drug candidate. The company’s virology projects, moreover, were going nowhere, with no commercially viable breakthroughs in sight. In 1968 Librium and Valium, followed by vitamin products and (in a respectable third place) sulfonamide antibacterials were Roche’s top sellers at the time. In the second half of the 1960s the focus was on expanding the portfolio to ease Roche’s overdependence on the risky benzodiazepine business. The Roche Research Management Group, composed of the heads of the research and manufacturing departments of the Swiss, US and British sites, demanded a new direction in research.
argued, biological research would need to be expanded at the expense of traditional chemical activities.

A more systematic search needed to be made for therapeutic agents using more efficient test procedures and better research into the biological causes of disease. Biology – for example, the study of bacterial metabolism – should be the starting point of all drug development. Precisely because of the tougher testing requirements for drug approval, development costs had risen enormously; Roche had to have a clear idea of the pharmacological action of a substance in the human body at the very outset of the research process.

The chemists counter-attack

The chemists launched an energetic counter-attack against such visions of the future. Otto Isler, an outstanding vitamin researcher and head of the Chemical Research Department, pointedly reminded his colleagues of the importance of chemically produced medicines and their commercial success for the company. He protested strongly against biological theories and speculations, which in his view had little to do with reality. Isler, however, was also well aware that there was money to be made from chemotherapy and had even championed tuberculosis research at Roche. Arnold Brossi, head of Chemical Research in Nutley (USA), also voiced a certain scepticism about the biological approach, arguing that Roche’s success and good name were built on discoveries in conventional synthetic chemistry and that major investments in biological research would be misplaced. However, subsequent developments showed the chemistry proponents to be on the defensive. This became strikingly apparent in 1967, when Alfred Pletscher became the first physician and biomedical researcher to head Roche’s entire research organisation.

Otto Isler may have been subtly avenging the chemists’ cause when he later dismissed Roche’s contribution to Bactrim as negligible, giving most of the credit to Wellcome. In fact, the American biochemist George H. Hitchings, Head of Research at Burroughs Wellcome in Tuckahoe, New York, had for many years lobbied...
in vain for combining sulfonamides on theoretical grounds and on the basis of good animal studies. No-one believed him until clinical trials produced astonishing results. Hitchings was an important scientific flag-bearer for Wellcome, having also created the antileukemia agent mercaptopurine and pyrimethamines for the treatment of toxoplasmosis, and having been behind many other discoveries. For their contributions to the drug treatment of infectious diseases and malignancies, he and his colleague Gertrude B. Elion were awarded the Nobel Prize in Physiology or Medicine in 1988.

Roche was thus dealing with first-class scientists at Burroughs Wellcome.

**Trimethoprim from Burroughs Wellcome**

The antibiotic trimethoprim, whose action on bacterial infections was discovered by Hitchings and Elion in 1956, was patented in 1953. The medicine inhibited the folic acid metabolism of gram-positive and gram-negative organisms and was used by Burroughs Wellcome to treat uncomplicated urinary and respiratory tract infections. In the early 1960s, very intensive research contacts began between Wellcome and Roche. Wellcome had previously made unsuccessful offers to work on trimethoprim with the Basel-based companies J. R. Geigy AG and Ciba AG. Both had refused, as they regarded the drug’s toxicity as unacceptable. Even in 1963 when Wellcome approached Roche, there was still considerable scepticism, particularly among microbiologists. Clinicians, however, were rapidly won over by the antibiotic’s bactericidal activity. Research management was also receptive given the success of Roche’s previous ventures into chemotherapy. Drugs like Gantrisin, Rimifon, Madribon and Gantanol accounted for a significant share of the company’s sales and profits. However, an internal memo in the mid-1960s warned of the conditions prevailing on the anti-infectives market in general and the sulfonamides market in particular. Management was also worried that the sulfonamides were losing ground to antibiotics. Roche’s Fansil (sulfadoxine) was a sulfonamide with some completely new properties, so that it was difficult to predict its chances on the market. That said, the positive features outweighed the negative, making it a valuable medicine with good commercial potential. Fansil was later designated by the World Health Organization (WHO) as an essential medicine, particularly for cholera.

The pressure was now on in Basel to discover and test more effective drugs and introduce them into clinical use. Six months of laboratory tests eventually revealed that a combination of the antibiotic trimethoprim (TM) and the sulfonamide sulfamethoxazole (SMZ: Gantanol) had some very special properties.

Antibacterial activity in Petri dishes proved astonishing and extremely interesting: the potentiation of two antibiotics at first appeared incredible and unprecedented.

**Astonishingly active combination**

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Extensive laboratory tests showed trimethoprim and sulfamethoxazole to be active, both alone and in combination, against a number of appropriately stained gram-positive and gram-negative bacteria. Pathogen-free areas on the test plates were larger with the combination than with the individual compounds. Experiments in mice infected with the bacterium *Escherichia coli*, the most common causative agent of intestinal infections, yielded the same result. Potentiation was also seen in mouse studies with *Streptococcus pneumoniae*, the most common pathogen in pneumonia and also responsible for other infectious diseases such as meningitis and endocarditis. The researchers were impressed not only by the intensity of activity of the trimethoprim and sulfamethoxazole combination, but also by its spectrum, which

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44 Isler (1971), 21f.
46 Founded in 1758, from 1970 Ciba-Geigy AG, from 1992 Ciba AG, since 1996 Novartis AG.
47 Founded in 1883 as Gesellschaft für chemische Industrie Basel, from 1945 under the name Ciba, from 1970 Ciba-Geigy AG, from 1992 Ciba AG, since 1996 Novartis AG.
48 Roche, Internal Memo No. 366.
49 Briefing minutes, 29 September 1965.
50 WHO Model Lists of Essential Medicines. See www.who.int/selection_medicines/committees/expert/16/applications/FDC_622.pdf
encompassed an extremely broad range of pathogens and was at least equivalent to the broad-spectrum antibiotics of the day, such as ampicillin, the tetracyclines, penicillin G, chloramphenicol or phenethicillin. A wide range of bacteria responsible for infectious diseases of the respiratory tract, gastrointestinal tract, urogenital tract, skin and soft tissues, as well as other infections, proved susceptible to the new combination product.52

 Cooperation between the two companies soon intensified; there were constant meetings in Basel and London. In the summer of 1966 the then 44-year-old microbiologist Erika Böhni presented her research results. She had learnt her English paper off by heart and accompanied it with some impressive slides. According to Böhni’s diary, Emanuel Grunberg, Director of the Department of Chemotherapy at Nutley, was ‘so pleased and excited that he stood up and said he had no idea that we were doing something like this’.53 The usually reticent Giuseppe Reggiani, one of the foremost clinical researchers at Roche, nodded to the speaker for the first time.54

 The contract with Wellcome was ultimately to include three specifically named pyrimidine potentiators from Wellcome and twelve sulfonamides from Roche. Both parties undertook to inform one another of any new advances in formulation development or dosages. Provision was also made for the exchange of scientific findings, although great care was taken in Basel to limit disclosures to information and compounds that were actually covered by the collaboration.55

 As research-based companies, Roche and Wellcome had similar pharmacological expertise and possessed similar medically focussed corporate cultures. Both companies were among the most important players in the global pharmaceuticals industry and strove for pharmacological excellence. The research departments and their philosophies, in particular, had a similar orientation. Yet obviously there were considerable cultural differences between the London-based company founded in 188856 and the pharmaceutical plant that had opened on the banks of the Rhine in Basel in 1896. The negotiating partners in the British metropolis displayed cosmopolitan refinement. ‘There was a genteel air about Wellcome that somehow echoed Britain’s colonial past. For the Baslers, with their ‘rather simpler, more republican tastes’ there was something vaguely imperial about all the mahogany and marble in Wellcome’s offices.’57 They were extremely impressed by the sumptuous surroundings and found their British hosts ‘polite, nice, but firm and precise, they just say things so quietly and politely’, as Erika Bohni commented in her diary. Later she remarked: ‘It strikes me in particular how composed Wellcome are in their dealings, how sure and how calm they are, even in the most threatening situations. And for this reason they will one day again hold the world in their hands, because of this superior calm, rooted in the ancient practices of a trading nation. There are pirate types among them too, with razor-sharp minds, who never forget themselves and flare up suddenly, “but we shall go ahead”’.58

 Ultimatum from London

 In autumn 1967, the ‘Antibacterials’ Project Group was formed in Basel and responsibility for it was entrusted to the microbiologist Erika Bohni. The group’s main task can be summed up in a few words: to defend Roche’s sulfonamides and look for new antibiotics.59 Bohni herself was initially worried about trimethoprim’s toxicity: specifically, she was afraid that potentiation of activity might entail potentiation of toxicity. However, laboratory tests of the combination of trimethoprim with Gantanol’s active ingredient, sulfamethoxazole, yielded increasingly persuasive results.

 It was soon found that a combination of five parts sulfamethoxazole to one part trimethoprim could be administered in such small quantities that toxicity appeared acceptable. However, even the first clinical trials failed to convince the critical scientists and they were afraid that trimethoprim might jeopardise the sulfonamide Gantanol and, with it, Roche’s good reputation. Despite Erika Bohni’s growing enthusiasm, those urging caution were extremely impressed by the sumptuous surroundings and found their British hosts ‘polite, nice, but firm and precise, they just

So effective did the antibacterial activity prove to be that some Petri dishes in which the inhibitors were being studied remained completely clear of bacterial growth. However, the researchers did not know whether the tests would ever lead to a commercially viable product.60

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53 Böhni, E.: Diary No VIII. Manuscript 27 June 1966. (no page). Erika Böhni’s estate papers held by Ernst Böhni, Stein am Rhein. I am most sincerely grateful to councillor Ernst Böhni for allowing me to examine the diaries. Ibid.
54 Roche, Internal Memo from M. Fernex and H. Neumann, 10 December 1975. RHA FE.2.1 – 103531 o.
56 Ibid.
57 (A woman of substance) (1903), 45.
In 1967, the straight-talking farmer’s daughter Erika Böhni stood before a virtually bare field. True, she had six years of experiments with the combination of trimethoprim and sulfamethoxazole behind her; but nothing had yet been published. The spring of 1969 became the busiest period of her life. Easter, Ascension, Whitsun, absolutely every free weekend, were devoted to preparing publications, presentations and reports. Working fast appealed to her; faced with overly punctilious indecision, she could become totally impatient. By dint of stubborn research, publications and lecture trips, Erika Böhni became Bactrim’s most important champion – in a sense she was the ‘face’ of Bactrim. Roche colleagues sometimes even referred to her as ‘Miss Bactrim’. Born on 13 January 1922, the daughter of a farmer and niece of a doctor in the small town of Stein am Rhein, throughout her life she retained an unmistakeable Schaffhausen dialect. Here was where she grew up and attended primary school and subsequently the cantonal school in Schaffhausen. From 1941 to 1947 she was one of the very few women to study biology at the Swiss Federal Institute of Technology in Zurich, where she also acquired a solid training in chemistry, and graduated in 1949 with a thesis on bitter rot fungus in cherries. After working for short periods in a few small companies, the 29-year-old joined Roche in 1951 and was to remain there for a full 33 years until retiring in 1984. She began as a member of the Basel-based tuberculosis research unit under Bernhard Fust. The antituberculosis agent Rimifon, launched by Roche in 1952, was such a great scientific advance that in subsequent years it became a secure basis for the department and a global calling card for Roche in the field of antibacterial chemotherapy. The chemotherapy unit was initially housed in the ‘Glaser Villa’, later replaced by Building 70, on the banks of the Rhine. ‘Fräulein Doktor Böhni’ ruled her laboratory on the ground floor of the research building with a firm hand. She was a respected and sometimes even feared individual, energetic, tireless and temperamental. Never one to hold back with her views, she expressed herself bluntly and directly. As a woman of substance and common sense, she was the third female Roche employee to rise to senior management level in the male-dominated company.

Glaser Villa (Building 23) at Roche Basel, with Building 62 in the background (1962). Originally a private residence, the villa was converted by Roche into laboratories and offices, then demolished in the 1960s. It was the first home of the newly established Microbiology Department headed by Erika Böhni.
the laboratory on Saturdays and Sundays as well. By her own account, however, Bactrim marked the pinnacle of Erika Böhni’s scientific career. In her enthusiasm about the mutually potentiating actions of sulfamethoxazole and trimethoprim, she said in retrospect: ‘People thought, old Böhni’s gone mad now. Until the fact was then confirmed by other bacteriologists. It was a wonderful and exciting time.’

In retirement, Erika Böhni abandoned her microscope for good. Refusing to look at another microbe, she turned her attention instead to plants and animals and their complex independences. Back in her stately parental home in Stein am Rhein, she wrote a 77-page children’s book about the grey heron, a common sight in the Rhine valley. The book was prompted by nature outings with her great-nieces and great-nephews, with the author trying to express scientific findings in neither too simple nor too complicated a manner, although it must be admitted that this project with illustrations in the author’s own hand cannot exactly be described as a truly successful child-friendly work. Erika Böhni died on 3 February 1999 at the age of 77 years in her family home.

launch the product on its own. Suddenly the project assumed a sense of urgency. The commercial department was adamant about not wasting all the energy invested so far.73 This meant an enormous effort on the part of Roche Basel. After a low point in the years 1964/65, chemotherapy again became a focus of research expenditure and staffing in this area was increased.72 Following a discussion with director Otto Isler, who recognised Erika Böhni’s all too heavy workload as well as her importance to the project, Böhni confided in her diary: ‘I note that a lot is expected of antibacterial chemotherapy.73

Essentially more a ‘do-er’ than a researcher, Böhni showed herself to be totally in her element in moving the new product forward and to be entirely up to the task.70 Once convinced, she brooked no resistance. In Basel rapid, energetic action was now the order of the day. For when the time came to divide up the launch markets, Wellcome’s comparatively limited geographic reach became apparent. Roche, by contrast, had steadily built a dense global distribution network since its founding in 1896 and hence would clearly have the lead role in the market rollout.73 In many countries – such as Great Britain or New Zealand – a joint launch of Bactrim and Septrin was agreed.

Encouraging clinical trials

The combination of sulfamethoxazole and trimethoprim in a five to one ratio produced extremely good results in the Basel laboratories in 1966, prompting the start of clinical trials. It was now apparent to research management that the combination met a number of the requirements for a broad-spectrum chemotherapeutic agent.76 The new product with its astonishingly potent bactericidal effect appeared capable of at least defending Roche’s share of the sulfonamide market, if not expanding it. Gantrisin and Gantanol were showing favourable growth, but the long-acting sulfonamides were at that time falling somewhat into disrepute because of their alleged adverse effects, such as severe allergic cutaneous and mucosal reactions (Stevens-Johnson syndrome) or extensive bullous detachment of the epidermis (Lyell syndrome). Roche was obliged to recognise with some concern that the authorities in some countries were restricting the drugs’ indications, which soon dented the sales of Madribon (an anti-infective agent for cholera and leprosy, among other diseases). The aim was to refute such criticisms as rapidly as possible with appropriate working parties. The sulfamethoxazole/trimethoprim combination, which opened promising vistas in human and veterinary medicine, therefore represented an all the more welcome expansion of the indications for sulfonamides.77 Then, in the second half of 1968, Roche was pleased to observe signs of a change in attitude towards long-acting sulfonamides on the part of certain health authorities (including those in the USA). The hope was therefore for a more sulfonamide-friendly future.

Following the results of trials in more than 1,000 patients, it was decided on 4–5 December 1967 to continue trials in Basel with only the five to one ratio of the sulfamethoxazole/trimethoprim mixture, predominantly as tablets of 400 mg Gantanol plus 80 mg trimethoprim. At the same time, Burroughs Wellcome made it clear that London intended to launch this combined form at the earliest possible opportunity – from about September 1968 onwards. Roche Nutley meanwhile continued clinical trials with Gantrisin (sulfisoxazole)/trimethoprim combinations in 20 to 1 and 10 to 1 ratios, while the other Roche centres intensified and extended the clinical trials of the new tablets together with Burroughs Wellcome. The following indications were proposed initially: urinary tract infections, chronic bronchitis and other bacterial infections from all clinical specialties. The new drug’s broad spectrum was meant to compete directly with conventional antibiotics. Comparative studies were declared to be entirely desirable.79

The intention was always to launch the new medicine in parallel with Burroughs Wellcome. Although the pricing situation for the launch of sulfamethoxazole/trimethoprim was not ideal, a decision (supported by the commercial department) was made in early 1968 to conduct large-scale clinical trials of the product with the dosage forms defined jointly with Burroughs Wellcome (solid oral form with 400 mg sulfamethoxazole plus 80 mg trimethoprim as well as a suspension syrup with the same dose ratio) as previously planned and to press on with these as rapidly as possible. Tablets were used provisionally, but the intention was still to ascertain whether two-piece capsules or capsule-shaped pills should be tested as a commercial form instead.80

In the course of 1968, a number of clinical trials were conducted with the combination in various hospitals and the results overall proved remarkably positive. Internist Paul Schnaas at Waid City Hospital in Zurich eliminated the symptoms of...
chronic urinary tract infection in six out of seven patients in ten days.81 Encouraging results followed in April 1968 from Innsbruck, Marseille, Glasgow, Vienna, Wulfrath, Interlaken and Belp. The clinical trial was conducted in ‘Basel countries’, meaning the smaller markets in Europe, Africa and the Far East that Roche supplied directly with its products, using ‘drapsules’ (an elongated film-coated tablet developed by the company); only Roche London retained the tablets because of the threatened loss of time. A useable syrup form was not yet available and the prototypes from Burroughs Wellcome proved completely unsuitable in terms of taste. The disks that had long been ordered from Wellcome were urgently required, since investigators in Germany in particular were demanding these test plates for detecting bacteria. In April 1968 Burroughs Wellcome decided on the brand name ‘Septrin’.82

‘Bactrim’ – a successful brand name

Statistics on the identity and incidence of pathogens targeted by the sulfamethoxazole/trimethoprim combination were first presented at Roche in early 1968 in a ‘Review of antimicrobial therapy’.83

By May 1968, Roche had a total of more than 640 evaluable cases with a 68% success rate. Urinary tract infections, chronic respiratory tract infections, gonorrhea and non-specific urethritis, in particular, were reliably eradicated or improved. The incidence of adverse reactions – predominantly cutaneous and hematological – was 4.3%. Bearing in mind that the patient population consisted principally of sulfonamide-resistant cases and the trial was performed in accordance with very strict criteria, the success rates achieved should be interpreted as signifying that potentiation of sulfamethoxazole by trimethoprim is also clearly apparent clinically.85

Testing of the combination was to be continued as widely and expeditiously as possible with the definitive drapsule dosage form containing 400 mg Gantanol and 80 mg trimethoprim; this was the only way in which the documentation required for registration and launch could be acquired on schedule. The situation was particularly pressing in Great Britain and New Zealand, as Basel wanted to supply those markets in parallel with Wellcome as soon as approval was forthcoming from the health authorities. Other markets would follow from autumn 1969 onwards. Roche’s energies were now clearly aligned behind the project. In addition to the indications that had already been investigated, research management wanted to clinically test and document activity against Streptococcus haemolyticus in tonsillitis, resistant staphylococci as causative agents of nosocomial (hospital-acquired) infections, gram-positive cocci, bacterial infections of the intestinal tract such as typhoid, paratyphoid, dysentery, salmonellosis and cholera, bacterial skin infections (dermatology, surgery) and malaria (acute attacks). Moreover, data on the fates of the component drugs in the body (pharmacokinetics) needed to be supplemented by appropriate studies with the combination. Lastly, publications needed to be prepared in readiness for launch.86

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bore the company code Ro 6-2580. Efficacy studies were planned comparing the sulfonamide combination with antibiotics. In mid-June 1968, it was decided that the Roche brand name for the sulfamethoxazole/trimethoprim combination would be ‘Bactrim’. Unfortunately we can no longer be sure who came up with the name.

What is clear is that it was a catchy, appropriate choice in any language, and expressed in a way everyone could understand what the medication was meant to do – combat disease-causing bacteria.

At that time, Burroughs Wellcome was already using the brand names ‘Seprin’ or ‘Eusaprim’; both in the UK and continental Europe. Derived from the septicemic (blood-poisoning) effect of microorganisms, ‘Seprin’ was undoubtedly inferior to the name ‘Bactrim’ from a promotional point of view. Roche’s commercial department consequently urged the earliest possible use of their own brand in publications even more vigorously, but according to information from the legal department at the time it could not yet be approved. The increasing number of reports coming in about the clinical uses of the product, such as from the Bernese spa resort Heiligenschwendi and from Lautergrund/Germany, Montevideo and Linz, continued to be encouraging. Doctors in Chile achieved particularly positive results in the enteric (typhoid) fever still widely prevalent in that country. They treated 15 children between the ages of one and a half and 13 years, with marked improvement in every case: ‘This result appears very favourable’, it was noted with relief in Basel. Moreover: ‘tolerability was excellent.’

87 ‘Antibacterials’ Project Group, Research Steering Committee, Dept. VI, 30 May 1968. RHA FE.0.3 – 103534 b.
88 VI/Klin. 10/68, 13 June 1968. RHA FE.0.3 – 103534 b.
89 Ibid, 5–6.
90 IV/Klin.14/68, 5 September 1968. RHA FE.0.3 – 103534 b.
Syrup, pediatric sugar-coated tablets, gelatin capsules, injections

By late June 1968, formulation scientists at Roche had developed a syrup formula which overcame the problem of the unpleasant taste by using an adsorbate of clay minerals (bentonite or Veegum [magnesium aluminium silicate]). Before the syrup could be released for general clinical trials, however, the release of the active ingredients from the adsorbate in the gastrointestinal tract had to be tested by measuring their levels in the blood. Once again research management highlighted the urgency of acquiring sufficient data on the pharmacokinetics of the sulfamethoxazole/trimethoprim combination in humans.91

In August 1968, the prototypes of a new pediatric form were available. The sugar-coated tablets contained only a quarter the amount of the active ingredients (100 milligrams of sulfamethoxazole, 20 milligrams of trimethoprim) and were correspondingly smaller.92 In the same month, the British regulatory authorities (Dunlop Committee93) granted approval for the licensing of Gantanol/trimethoprim as a pharmaceutical product. Burroughs Wellcome and Roche were thus able to launch the combination jointly in October 1968 in Great Britain.94

Roche agreed with its British counterparts to use the abbreviation TMP 1 / SM 5 for the sulfamethoxazole/trimethoprim combination in publications.95 As was conceded with some dissatisfaction in Basel, this decision meant a victory for Wellcome because trimethoprim was named first. At the beginning of October 1968, it was reported that work was continuing on dosage forms, specifically on granulated two-piece gelatin capsules. The fill volume per capsule was 520 mg and they were manufactured...
with a Höfliger & Karg machine. The same active substance granules with the addition of glidants and lactose granules could also be obtained on a Parke-Davis machine in size 0 gelatin capsules and a capsule fill volume of 565 mg with an extremely fast filling rate. Both types of production had been undergoing stability testing since the summer of 1968. During the month of November the original capsules came in a deep yellow-dark grey colour and filling was being tested on the Zanasi capsule filling machine.

Solutions of the therapeutic agent for injection posed difficulties because of poor and variable solubility and variable solution pH. In addition, studies were needed on the irritant effect, miscibility in blood and toxicity of the injection presentation. Following completion of these studies, the research department would decide whether there was any value in continuing work on the solution. The ingestion of Bactrim as a suspension syrup and its absorbability with Veegum adsorbate had yet to be studied. There was also interest in a suppository form, even if rectal absorption of Gantanol had initially proved unsatisfactory, and this required the testing of various suppository bases.

### Treatment successful in 77% of cases

In mid-November 1968, discussions revealed that Burroughs Wellcome wanted to launch sulfamethoxazole/trimethoprim in continental Europe as soon as possible. Roche, on the other hand, adopted a more reticent approach because it felt that more documentation would be needed for registration in other countries, particularly on toxicity, hematotoxicity and comparative efficacy versus other antibiotics, etc., than those submitted to the British Dunlop Committee. Because of Burroughs Wellcome’s firmly expressed intentions, however, Roche considered itself obliged to launch Bactrim, at least in Germany, with as little delay as possible. In view of the good correlation between experimental data and clinical effect, plus the number of patients who had undergone long-term treatment for two years with no significant toxicity, Roche eventually saw no further obstacles to moving up the launch. All the papers being prepared on Ro 6–2580 were now to be readied for publication as soon as possible.

Some concerns still remained, however, about negative genetic effects. Research management demanded studied demands of the effect on chromosomes. Research on human connective tissue cells (fibroblasts) was also considered mandatory. It had in fact been established that the trimethoprim component caused malformations in animals at 15 times the therapeutic dose. Dr Staiger from Roche Laboratories, partly in association with Werner Schmid from the Genetics Laboratory at the Zurich Children’s Hospital, studied the effect of the individual Bactrim components on chromosomes outside the body (in vitro, i.e. in the test tube) and in the living organism (in vivo). By late November 1968, the ‘Chemotherapy’ work group had before it the results for tablets and drapsules from 61 Roche-sponsored investigators in 15 countries. A total of 834 patients were evaluable for therapeutic efficacy and 918 for tolerability. The dosage was in most cases one or two, and in exceptional cases three, drapsules or tablets twice daily. The treatment duration was generally five to ten days, but could be as long as 50 days. In 642 of the 834 therapeutically evaluable cases outcome was good or at least partially successful. This equated to an overall success rate of 77%. Burroughs Wellcome obtained about the same mean success rate of 78% with a database that included 893 patients. Most of the treated cases involved urinary or respiratory tract infections. There were a significant number of urogenital infections, particularly among Wellcome’s patients, and the data also included non-representative numbers of cases of scarlet fever and other ear, nose and throat infections, intestinal infections including typhoid, skin infections, purulent meningitis and gonorrhea. Comparative trials versus conventional antibiotics were in progress in several countries. Adverse effects in the 918 evaluable Roche cases included 3.38% gastrointestinal symptoms, 2.07% skin reactions, 0.22% other allergic symptoms, 0.98% hematological reactions, and 0.33% miscellaneous effects. Wellcome reported no hematological effects but did not perform regular blood counts; the 1% skin reactions all proved to be mild in nature.

In view of the pressure from Wellcome, Basel decided to schedule the launch of Bactrim in Switzerland and Germany for the spring of 1969. Once again the laboratories were urged to provide documentation as soon as possible for the additional disease indications that had still not been confirmed, as well as supplementary studies on pharmacokinetics and metabolism. The proposed Bactrim syrup with a Veegum adsorbate base required a clinical trial beforehand, involving blood level monitoring of drug release in the gastrointestinal tract. Wellcome’s suspension syrup was not adsorbed to Veegum, but instead suspended freely. The Roche product was also somewhat bitter. However, Basel noted with satisfaction: ‘The Burroughs Wellcome Septin suspensions, on the other hand, are incomparably more bitter.’

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96 Company founded in 1948 in Waiblingen which manufactured packaging machines for dry pharmaceutical products and which was taken over in 1970 by the Bosch group.
97 Founded in 1866/67 in Detroit and formerly the largest drugmaker in the USA, now part of Pfizer.
98 According to the packaging company Zanasi Fratelli P.r.L. in Sassuolo (Modena/Italy).
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Comparable to conventional antibiotics

Roche management was fully aware that if the company could provide objective data showing Bactrim to be at least equal in therapeutic effect to established antibiotics in some major indications, this would give the product enormous commercial potential: ‘Further comparisons with standard antibiotics are therefore urgently required. They should preferably be conducted as double-blind trials.’ These trials proved extremely challenging because of the difference in dosing intervals between test and comparator products. Chloramphenicol105 (effective against typhoid, cholera and urinary tract infections) and tetracycline106 (effective against respiratory tract and urinary tract infections) were regarded as first-line reference products.107

Roche intended to continue performing bacteriological studies as part of its clinical trials programme until the product was launched, and then restrict itself to providing an advisory service to hospitals and scientific institutions. Dissemination of the disk test was to be entrusted largely to the highly experienced Oxoid company108, which at the time already had a combination disk in its range of products. New methods were developed for a more detailed pharmacokinetic study. In the veterinary sector, Wellcome’s combination product underwent clinical testing in dogs and cats with the aim of recommending it for small-animal use in the UK. Supporting publications were expected to be ready in 1969. Roche adopted a wait-and-see approach towards these trials, but if necessary would be able to build on the Wellcome studies.109

In October 1968, the sulfamethoxazole/trimethoprim combination was launched on the British market simultaneously under the brand names Septrin (Wellcome) and Bactrim (Roche)110. The Wellcome Foundation in London then set up a Clinical Information Department (CID) – a development watched in Basel with admiration and a touch of envy. The rationale was that global interest in this new antibacterial combination product was so great that the company wished to track and support publications more professionally.111 Roche submitted the registration dossier for Bactrim to the German Federal Health Agency in mid-December 1968. At the same time, the spectrum of indications was also extended to include milder and acute infections and clinical trials to this end were intensified worldwide. The Basel team hoped to have sufficient data available for this extended range of indications in 1969 to obtain approval in most countries. Various publications on the many in vitro and in vivo experimental findings were in preparation. Roche laid particular stress on the effect of sulfamethoxazole in the combination, since Wellcome – as the Baslers peevishly remarked – exclusively highlighted the effects of trimethoprim.

Roche’s annual report for 1968 informed customers and staff for the first time about a ‘novel therapeutic approach’, the ‘combination of one of our well-established sulfonamides with the...’

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105 Broad-spectrum antibiotic, first obtained in 1947 from Streptomyces venezuelae.
106 Broad-spectrum antibiotic, produced from Streptomyces aureofaciens, described in 1948, patented in 1955.
107 VI/Klin. 20/68, 19 December 1968, 1. RHA FE.0.3 – 103534 b.
110 Minutes No 4, Research Steering Committee, Department VI, 30 January 1969. RHA FE.6.3 – 103534 c.
pyrimidine derivative trimethoprim’. The new medication, the report said, was being supplied to the medical profession under the brand name ‘Bactrim’. While the indications had initially been limited to severe urinary and respiratory infections, there was a growing body of evidence of the drug’s therapeutic value in other infections.112

Feverish publication activity in 1969

Throughout 1969, the Basel research department was busy preparing regulatory filings for Bactrim.114 At the same time, intensive analyses, coordination meetings, conferences and congresses were in progress. Reports continued to come in regularly from doctors from around the world about treatment outcomes with Bactrim. On 18 February 1969, Erika Böhni briefed managers from Wellcome on launch activities for Bactrim. This led to tensions over the assessment of the two components. London complained that Roche’s German filing depicted the bactericidal trimethoprim merely as a potentiator of the sulfonamide Gantanol (sulfamethoxazole), whereas in Wellcome’s view trimethoprim was the more important component of the combination. The Basel delegation countered that the experimental and clinical evidence clearly showed the two components to be of equal importance. Moreover, trimethoprim monotherapy had been too highly dosed for years, had proved toxic and consequently had been rejected by the medical profession.115 Subsequently, and with some urgency, Roche undertook research into the structures of the trimethoprim metabolites, which it had already confidentially disclosed to a number of outside researchers.116

A joint Burroughs Wellcome and Roche symposium in the UK on 31 March 1969 showed that Basel was somewhat behind in terms of publications; Roche was only able to present two experimental and six clinical papers, versus two experimental and nine clinical papers from Wellcome.117 Moreover, the Roche representatives were obliged to note, to their annoyance, that the

115 ‘Antibacterials’ Project Group No 2/69, 18 February 1969, 2. RHA FE.0.3 – 103534 f.
117 Planning meeting minutes, 14 May 1969, 2.
partner company did not shrink ‘from exploiting the different pharmaceutical forms to their own advantage as well’. This involved trying to demonstrate that blood levels after the ingestion of drapsules were lower, somewhat later and more dispersed than after tablets. While Roche doubted whether the differences were biologically significant, it still feared they could be used as a dangerous marketing argument for Septrin. Roche also noted with displeasure that Burroughs Wellcome was seeking to achieve a competitive advantage with an additional syrup formulation for adults which, ‘in view of the special competitive situation, should not be allowed’. For this reason, Roche prepared to launch a syrup wherever its partner company was doing so.119 Trials showed that the syrup could be stored just as well in glass as in plastic and that it exhibited equally good bactericidal activity as well as the same weak to nonexistent fungicidal activity.120

In 1969, Roche produced the following dosage forms for Bactrim: a suspension syrup, particularly for children, with 200 mg sulfamethoxazole and 40 mg trimethoprim per 5 ml; a solution for injection with a recommended dose of 400 mg sulfamethoxazole and 80 mg trimethoprim per 5 ml; suppositories containing 400 mg sulfamethoxazole and 80 mg trimethoprim; film-coated tablets (drapsules) containing 400 mg sulfamethoxazole and 80 mg trimethoprim,121 Owing to production constraints, round sugar-coated tablets replaced the film-coated drapsules in some markets, notably Switzerland, the Benelux countries, Latin America, Spain and Turkey. Drapsules continued to be supplied in Great Britain, Germany, France, Austria, Australia and the Far East, however.122

With ‘optimism’ and the ‘necessary aggressiveness’

A symposium for doctors on Septrin and Bactrim organised by Wellcome was held on 9 May 1969. Erika Böhnι123 and Daniel E. Schwartz124 spoke on behalf of Roche and George H. Hitchings125 and S. R. Bushby on behalf of Wellcome. Basel anticipated the meeting with future Nobel prizewinner Hitchings and the equally excellent bacteriologist Bushby with some anxiety. Admittedly, Wellcome was at that time informed of the status of research in Basel on trimethoprim metabolites, but the ongoing studies could not be made public until the effects and patentability of the newly isolated, synthetic products had been elucidated. It was agreed at Roche to refer only to ‘new substances’.127 The graphic designers had produced their own lavish coloured slides for Erika Böhnι to illustrate the findings from mouse studies. By her own account, the speaker had ‘not the slightest fear’ and assessed the Wellcome speakers who preceded her as ‘run of the mill, their slides hard to understand, way over the top for these doctors’. Her own presentation, however, she regarded as totally successful: ‘My paper with its simple words and new pictures went down like a bomb. Everyone was delighted and women even told me in the toilet that they had understood every word’. While Erika Böhnι continued to get on extremely well with the British, she was irritated by her colleagues in Basel: ‘The Roche people particularly get on my nerves, they are always looking worriedly over their shoulder when somebody asks them something. They like to put on an act, think the worst of everything and want to show what brilliant debaters they are. […] We are much too weak for Burroughs Wellcome, who definitely chose Roche for psychological reasons because they could just do what they want with them. And in that they have completely and utterly succeeded.’129 In this respect, the exceptional microbiologist was to be proved wrong. The Basel team held its own in the Bactrim project – and, unlike Burroughs Wellcome, Roche still exists today as an independent company.

116 Ibid., 2.
117 PA meeting minutes No 5, 13 January 1970.
118 Roche, Internal Memo No 942, 6 November 1970. RoA FE.2.1 – 103531 o.

120 Roche, Internal Memo No 942, 6 November 1970. RoA FE.2.1 – 103531 o.

121 VI/Klin. 7/69, 24 April 1969, 1. RHA FE.0.3 – 103534 f.
122 VI/Klin. 2/69, 6 February 1969, 3. RHA FE.0.3 – 103534 f.
127 ‘Antibacterials’ Project Group, Minutes No 1/69, 12 February 1969, 3. RHA FE.0.3 – 103534 f.
129 Ibid.
On 14 May 1969, Bactrim was discussed at a planning meeting with 25 participants at the Basel head office. Experience in the UK showed the product’s great potential. But partnering with a competitor posed some unusual marketing challenges. It was a task to be tackled ‘with optimism, but also with the necessary aggressiveness, giving due regard to our partner but also to our own sulfonamides.’ Conventional sulfonamides and antibiotics admittedly seemed likely to lose some of their mythical status. However, for precisely that reason, the market situation appeared propitious for the launch of a novel antibacterial preparation. Unfortunately for Roche the joint venture with Burroughs Wellcome gave the British some advantages. They were the ones who had developed the product’s new component—a fact they exploited to the full, much to Roche’s displeasure. Nevertheless, the Basel company believed it had the stronger marketing organisation. And far from playing down Wellcome’s ‘trimethoprim story’, they recognised that they could turn it to their advantage by emphasising their own role in making trimethoprim a viable therapeutic by combining it with a sulphonamide…

Roche had opted for the novel drapsule dosage form for Bactrim in 1967 on the grounds that it was more in line with the modern image of antibiotics and differed fundamentally from the conventional tablet form at Burroughs Wellcome. Because of production constraints, however, the Basel team was unable to get its way. The formulation department for investigational products accordingly proposed abandoning the drapsule in most countries and launching the product as a sugar-coated tablet instead, unless launch preparations were already well advanced. And even this limited retention of the drapsule needed to be reviewed, since according to the latest market research ever more antibiotics were coming onto the market in tablet form. Because tableting machines were also to be found in all Roche manufacturing plants, it was decided generally to switch to the tablet form for Bactrim. Erika Böhni commented in her diary with her customary acerbity on the tenacious adherence to the drapsule and the subsequent capitulation: the men at Roche did not realise ‘how ridiculous they have made themselves with their drapsules, we cannot fight it.’ In May 1969 there were plans to introduce Bactrim in a number of countries by year’s end, including Switzerland, Cyprus, Lebanon, Germany, Australia, and possibly Spain, Argentina and Brazil, as well as some Middle and Far Eastern countries.

As far as promoting the new product was concerned, the big challenge was to communicate Bactrim’s extremely broad spectrum of uses. ‘Bactrim—the third generation in bacterial chemotherapy’ was adopted as a suitable general marketing slogan. Sulfamidochrysoidin (Prontosil) from 1935 had been the first generation and sulfamethoxazole (Gantanol) from 1962 the second. It was now a matter of highlighting what was novel about Bactrim. To this end, the planning meeting remarked: ‘The trimethoprim story cannot therefore be avoided. It must be exploited as positively as possible to our benefit.’ The product’s mutually potentiating active ingredients and resulting bactericidal effect thus had to figure prominently in all promotional claims. As a broad-spectrum chemotherapeutic, Bactrim could be recommended for severe and for milder cases.

Launch in hospitals, doctors’ offices and pharmacies

Because Burroughs Wellcome had largely succeeded in winning over British hospitals to Septrin through early initiatives and greatly expanded clinical trials, Roche wanted to extend its own on-going clinical studies, at least in Germany and Switzerland. The company also wanted to press ahead with patient trials in Argentina, Brazil and Spain, as well as in the Far East. In Switzerland, hospitals down to district level were provided with simplified information material and questionnaires, while in Germany the number of hospitals was expanded to 300 for the extended trials. Three thousand German doctors were to be supplied six weeks before launch with enough Bactrim to treat 30 patients each. In keeping with custom, Roche supplied pharmacists with an ‘original pack’ of the product for each dosage and pack size.

In May 1969 Burroughs Wellcome delivered 1000 kg of trimethoprim to the Basel Production Department without a hitch. The glaring lack of scientific publications caused more headaches. In the spring of 1969 eight scientific papers were pending, but none would be ready for print until a year later. This resulted in the unsatisfactory situation that at the time of the launch in Switzerland not a single publication was available: ‘Urgent reactivation of these studies is therefore indicated.’ Basel was seriously concerned that Burroughs Wellcome was already making media hay out of a minimum of clinical cases and wondered whether Roche ‘should not also be somewhat more enterprising in this respect’. On the initiative of Roche.

Grenzach, nine articles also appeared in a special issue of the journal Chemotherapie geared to doctors in conjunction with the launch programme. It included a contribution by Erika Böhni on bacteriology.

Bactrim/Septrin’s impressive debut on the British market was reported at the annual Roche Research Management Group meeting in St. Moritz from 11 to 16 June 1969. During the meeting management also declared itself ready to defend Roche’s position against Wellcome. A general decision was taken to continue sulfonamide research. Pharmacological, clinical and metabolic studies on Bactrim would be pursued in Basel. Clinical trials on 2500 patients had produced good results in respiratory and urogenital indications. The time had come to test the mode of action against additional more serious diseases such as typhoid, cholera, osteomyelitis and meningitis. Research management noted that Wellcome was also planning to launch the trimethoprim/sulfamethoxazole combination as a veterinary medicine for dogs and cats. This was not a cause for alarm as Roche had little interest in the veterinary market. Management was also aware that in the first few years after launch nearly as many tablets would be dispensed as free samples in some countries as were sold. This was considered acceptable in view of the special challenges
of a double launch and a reasonable return on investment was expected despite the financial costs.\textsuperscript{143}

An attractive illustrated launch booklet on Bactrim appeared in a number of different languages at the end of 1969. It comprised 84 pages and in a series of key messages promised a targeted advance in infection therapy, a completely novel mode of action, reciprocal potentiation and a broad-spectrum bactericidal activity against gram-positive and gram-negative bacteria.\textsuperscript{144} The booklet was divided into five sections and also contained a summary of key product information enabling the busy doctor ‘to use the product correctly after five minutes’ reading’.\textsuperscript{145} Doctors received no fewer than 27 communications about Bactrim in the first twelve months after launch, including a series of brochures and offprints. Four different types of advertisement in the most important medical journals were planned.\textsuperscript{146} However, it seemed impossible for the time being to produce special films on Bactrim for the mini-symposia that were planned.\textsuperscript{147}

Exhausting promotional tours

On 24 June 1969, a Bactrim Colloquium was organised in Basel for the supervisors of the ‘Basel countries’ and medical representatives in Switzerland. For the other medical representatives, colloquia were held abroad in the following months. About 1.85 million Swiss francs were spent on the launch campaign in the first year in Switzerland alone.

These were exhausting months for Erika Böhni. It was her job to establish a new sensitivity test for Bactrim in a wide variety of different laboratories. This required a specific medium that would vividly demonstrate efficacy and provide a suitably dramatic visualisation of the potentiating properties of the combination product. The Oxoid disks already mentioned fitted the bill. Placed on nutrient media, they made the bactericidal effect clearly visible. The launch of a laboratory method of this kind, however, was too challenging a task for a medical representative. Hence the reliance on Erika Böhni.\textsuperscript{148} Her comment on one of these events which she had to hold in Sweden appears typical of her: in Stockholm on 18 June 1969 it went ‘particularly well, because most of the people there were bacteriologists rather than bums on seats’.\textsuperscript{149} For the 6th International Chemotherapy Congress in August 1969, Böhni travelled to Tokyo and there too reported on her work with the Bactrim disks. Any pre-event anxiety was by her own account ‘not worth talking about: everything went well, with the microphone, with the images, I received applause like no-one else. Colourful, cheerful, clear: that always goes down well.’\textsuperscript{150}

After her paper Böhni received ‘the highest compliments’ and responded in true Roche fashion: ‘For a good company, I do a good job.’\textsuperscript{150}

The programme included presentations of clinical trial results, which were disputed by the local study coordinators.\textsuperscript{151} Erika Böhni later remembered with pleasure the friendly contacts with the Japanese people and her visit to the National Museum for Western Art: ‘I saw there the most beautiful Segantini I have ever seen in my life. You cannot find it in any catalogue, but I can still see it before me, it was simply wonderful.’\textsuperscript{152}
Further travel took Erika Böhni to the Netherlands, Italy and Greece, and in the autumn of 1969 to South Africa. The general manager there had prepared the 14-day tour along the East Coast like a military campaign and demanded that Böhni speak ‘longer and louder’. Recalling the experience, she said: ‘Every minute was booked up, from getting up until late after midnight: aperitifs, lectures, discussions with bacteriologists and clinicians. […] On the tenth day we finally collapsed. We simply couldn’t do any more.’ 153

Erika Böhni published an article in the ‘Schweizerischen Medizinischen Wochenschrift’ [Swiss Medical Weekly] comparing the antibacterial properties of conventional antibiotics with those of Bactrim. Using nutrient media and experiments in mice and rats she showed how the bacteriostatic/bactericidal activity of Bactrim against four bacterial pathogens was superior to that of the antibiotics oxytetracycline and chloramphenicol.154

In preparation for a global rollout, Roche continued to press ahead with the clinical trials needed to support individual national filings. Staff compiled reports on numerous experimental and clinical studies and delivered papers at conferences, symposia and congresses. In the Roche laboratories, researchers combined other sulfonamides with potentiators, albeit with rather more modest success.155 While the clinical trials in Belgium, Germany, France, Italy, Austria and Switzerland were very broad based, the number of trial sites in various other countries, particularly Australia, New Zealand, the Far East, the Netherlands and Scandinavia, was still unsatisfactory. For this reason, increased efforts were made there, ‘not least to prevent Burroughs Wellcome from gaining a head start in these areas’.156 Because of the competitive situation, attempts were made to achieve the widest possible dissemination of the product by way of a prelaunch campaign, although Roche also had to recognise that in some places testing had not been conducted in accordance with the strict criteria usually required by the company.157

Further launch activities

In 1970 Bactrim was registered in Germany under patent number 1,103,931 and a little later in Spain as well. The United States patent office awarded the drug a highly detailed patent (No 3,515,783) on 2 June 1970158 following a filing by Emanuel Grunberg159, a major tuberculosis researcher and head of the Chemotherapy Department at Roche Nutley. The Food and Drug Administration was primarily interested in the drug’s effects on pregnancy, which were investigated subsequently in numerous experiments and studies. There had in fact been no studies prior to that in pregnant women or women planning a pregnancy.160

Thanks to Bactrim, Ernst Wiesmann161, Full Professor of Microbiology and one of the most important bacteriologists in Switzerland, was persuaded to cooperate with Roche ‘after attempts to this end had been unsuccessful for years’. This key opinion leader appeared so important that he was remunerated for his comments on Bactrim with 1,200 Swiss francs and was paid the same amount as the monthly salary of a laboratory technician for a year.162

The annual meeting of the Roche Research Management Group, in June 1970 in Princeton/New Jersey, included reports on Bactrim’s global market uptake and tests with new dosage forms – a pediatric syrup and suspensions for adults and an intramuscular...
At a 1971 meeting in the English village of Broadway, the need to consolidate and extend Roche’s position in the field of sulfonamides relative to Burroughs Wellcome was re-emphasised in light of Bactrim’s growing success. The trimethoprim research in Nutley had done much to enable Roche to engage self-confidently with its counterparts. A workshop in Basel on 3/4 May 1971, at which the three Roche research centres were represented, examined the clinical progress that had been made and discussed further coordination. At a meeting in Basel on 28 July 1971 with C. Madden from Wellcome on the future of Bactrim/Seprin cooperation, Roche staff were decidedly reticent, whereas the Englishman proved astonishingly open in reporting on Wellcome’s lack of experience in the sulfonamide field; Madden admitted that Seprin’s market position was unsatisfactory outside Great Britain and that changes in personnel were looming. Basel doubted whether Wellcome would continue the joint venture if London had to play second fiddle in the long run.

A Bactrim Project Group was set up in-house to demonstrate in double-blind studies that the new medicine was more effective than comparable components and covered a broad spectrum of use. To her delight, Roche granted Erika Böhni an inventor’s share in Bactrim in 1971, the same year she was promoted to the senior management rank of Prokurist. Rank and file employees were also extremely proud of Roche’s new medicine. In a portrait of the penicillin pioneer Alexander Fleming, the Roche Zeitung in 1971 noted with satisfaction:

‘Together with England’s Wellcome Foundation, Roche has achieved the latest breakthrough in antibacterial compounds. Bactrim, a broad-spectrum bactericidal chemotherapeutic, is effective in infections of the skin, respiratory tract, kidneys and urinary tract, female and male genital tract and gastrointestinal tract.’

Expectations met ‘across the board’

Bactrim generated sales of 57 million Swiss francs in 1970 and more than double that, 118 million, in 1971. At 161 million Swiss francs, Bactrim sales in 1972 for the first time accounted for more than 5% of Group sales revenues. Undoubtedly, the anti-infective virus had gained considerable weight as a result of the encouraging success of the new product, even if Bactrim had overshadowed and supplanted the previous antibiotics. At the beginning of the 1970s, it became apparent that the medicine had moved into the front ranks of pharmaceutical products in numerous countries. The launch of Bactrim in more and more countries was commented upon with satisfaction in Basel: ‘This product meets expectations across the board.’ The 7th International Congress of Chemotherapy in Prague in August 1971 showed that Eastern European physicians also had a keen interest in Bactrim. The medicine rapidly established itself as the global treatment of choice.

At the research management meeting in June 1972 in Territet near Montreux, the participants from Roche Nutley were optimistic about the sales outlook in the US as well. Numerous documents needed to be submitted to the American authorities, as the European data could not be used in the United States. In Nutley, a new process for synthesising trimethoprim was discovered and underwent intensive study as Ro 20-5662. The company was intent on maintaining its market lead over Wellcome and for this reason thoughts were already turning in Basel to possible successors to Bactrim. In the longer term a successor product was also seen as a road to independence from Burroughs Wellcome. The metabolism of trimethoprim continued to be studied, and the four main metabolites isolated at Roche were synthesised in sufficient quantities for closer chemotherapeutic and toxicological testing. All four proved inferior to trimethoprim as potentiators. A single isomeric by-product initially appeared to be a promising, well-tolerated potentiatior. Despite these setbacks, Roche’s chemists continued their targeted search for new potentiators.

Various veterinary formulations, ranging from solutions for injection and tablets to powders for oral use and medicinal feed additives, were also investigated.
Roche Grenzach (Germany) studied the treatment outcomes and tolerability of Bactrim solution for injection in 668 patients. The 86% success rate was deemed ‘very satisfactory’, as was general and local tolerability. In 1973, the launch of the intramuscular form was also planned shortly in Switzerland.177 Reports of difficulties were immediately investigated at Roche. When the Düsseldorf City Hospitals reported cloudiness or sedimentation in the Bactrim ampoule solution, the mixture was immediately examined in Basel and the reason found to lie in the extremely high degree of acidity of the water used; a handling error could also not be altogether ruled out.178 In addition, the constantly increasing number of studies in numerous university hospitals was monitored closely, for instance for side effects.179

In 1973, Roche developed Kao-Bactrim with kaolin in syrup form for dysentery in children and adults. This antidiarrheal medication was particularly suitable for southern and tropical countries, whereas there was less interest in introducing it in Europe.180 Wellcome meanwhile was working on dispersible tablets with Primojel, a non-patentable product which nevertheless was declared a business secret.181

**Number 3 behind Valium and Librium**

In 1973 the annual Roche symposium in the spa resort of Hahnenklee in the Upper Harz mountains reviewed the bacteriology, pharmacology and clinical use of Bactrim.182 Meetings between the partner companies also continued in the mid-1970s. During this period they decided to cooperate closely on an Indian launch, discussed the pricing pressures being exerted by the US government and expressed indignation over the Norwegian authorities’ assessment of Bactrim/Septrin as a second-line medication.183 However, the association with Wellcome was a constant source of friction. In the spring of 1974 Roche’s executive management was deliberating how it could get a 34% reduction in the price it was paying Welcome for trimethoprim, and the feeling was that the reduction should apply to supplies to Roche’s Nutley affiliate as well. In addition, it was agreed that Burroughs Wellcome should launch Septrin in Pakistan, while Roche would supply the Iranian market with Bactrim. After Wellcome ventured into Iran anyway, Roche wanted compensation for Pakistan. Roche London had developed a water-soluble Bactrim tablet and wanted to introduce this rapidly ‘to steal a march on Burroughs Wellcome’. In view of the discussions about India and Pakistan, however, it was decided to wait two months – particularly because of India, where Wellcome was ready to launch, whereas Roche Bombay had not yet received marketing approval.184 In mid-1975 rumours were circulating at Burroughs Wellcome that Roche UK was pressing ahead with its own manufacturing process for trimethoprim and since February 1975 had felt free to produce the drug itself. Roche Basel assured Wellcome it needn’t worry as long as the prices for trimethoprim were reasonable.185

In 1974 Roche announced that Bactrim was doing so well outside the US that it had become the company’s third top-selling product, behind Valium and Librium. A broader range of indications in the US was considered highly desirable186 and was expected to boost sales further. (The drug had been available in the US since 1973, but only for urinary tract infections.) In 1975 new clinical trial data on Bactrim were reported at the Roche Management Meeting at Great Fosters, England, including reports on the use of tablets and pediatric suspensions in vari...
ous infections. Outcomes in bacterial dysentery and infections with the fungus *Pneumocystis carinii* (at the time regarded as a possible causative pathogen of pneumonia) were encouraging, as were the trial data in otitis media, meningitis and infections with *staphylococci*, *streptococci*, *Escherichia coli* and *Klebsiella*. Studies of 10- and 28-day courses of treatment for urinary tract infection showed better results with Bactrim than with other products. Results in chronic prostatitis were as striking as in gonorrhea. Work also continued on solutions for injection for use in severe infections. A Bactrim solution for intramuscular injection, for example, had been undergoing intensive clinical testing since early 1975. This was a 3 ml ampoule containing 800 mg sulfamethoxazole and 160 mg trimethoprim in a 52% glycofurol solution – double the quantities of active ingredient that would later to be marketed in tablet form as Bactrim forte. Efficacy and overall tolerability were ‘very satisfactory’ in 138 patients from eight countries. Kao-Bactrim syrup and Bactrim Balsamico were also being trialled – projects about which Basel chose not to share information with Wellcome.

The 9th International Congress of Chemotherapy in London from 13 to 18 July 1975 brought together 2000 specialists presenting almost a thousand scientific papers. At Roche headquarters it was noted with satisfaction that at least 60 of these related to Roche products, including more than 30 on Bactrim – Roche had clearly strengthened its reputation as a chemotherapy company. Meanwhile, cooperation between Roche and Wellcome on Bactrim and possible successor products remained close. For example, both companies were investigating another trimethoprim/sulfonamide combination: trimethoprim/sulfadiazine. There was an on-going search for new potentiators and scientific data were exchanged on the choice of the most suitable drug candidates. Participants at a joint meeting at the Burroughs Wellcome site in Beckenham, North Carolina, from 17 to 19 December, shared information on the latest animal experiments and the progress of research on the trimethoprim/sulfadiazine combination, on which they agreed to cooperate. Cooperation was also to be extended to include new potentiators.

Danger on the horizon: trimethoprim as single-agent therapy

In early 1976 Basel was somewhat concerned to note that trimethoprim had been commercialised by a Finnish company and that, in addition, efforts were underway by competitor companies to use trimethoprim as a single agent. Launch as a single-agent product undoubtedly represented a threat to Bactrim/Seprin, both to sales and to the combination as a whole. Roche wanted to make careful preparations for suitable countermeasures and even considered a precautionary application for trimethoprim as a single agent for very limited indications in the US. Ultimately, however, the company concluded everything possible should be done to prevent the launch of trimethoprim as a single agent.

The clinical results with trimethoprim alone were not very good, as studies of the literature showed. Erika Böhni wrote down her thoughts on this with her usual terseness (‘Please do not pass on to Wellcome’). She saw patent expiry as a possible reason for promoting the use of trimethoprim alone. They had been there before. Twenty years previously trimethoprim had been supplied alone in the US and later also in Switzerland. While

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187 Memo for the RRMG-Meeting 1975, 22 May 1975, RHA FE.4 - 103531 m.
188 Havas, L.: [Internal research report], 26 August 1975. RHA DE.2.1 - 103531 t,u.
190 [Reputation as chemotherapy firm enhanced]. Roche Nachrichten, October, 4/1975, 1.
191 [Cooperation with Wellcome in the area of Bactrim and possible successor products]. Internal Memo, 10 November 1975, RHA FE.2.1 - 103531 q,r.
192 M. Fernex and H. Neumann: [Cooperation with Wellcome in the area of Bactrim and possible successor products], Internal Memo, 10 November 1975, RHA FE.2.1 - 103531 t,u.
193 Note. Trimethoprim as a single speciality, 8 January 1976, RHA FE.2.1 - 103531 p.
194 Havas, L.: [The efficacy and tolerability of trimethoprim as an individual product (preliminary report)], 17 February 1976, RHA DE.2.1 - 103531 t,u.
there had been some therapeutic successes, severe adverse effects, including hematotoxicity and even deaths, had occurred. This was precisely why a sulfonamide had been added – it reduced toxicity without weakening chemotherapeutic activity. Citing the countless chemotherapeutic tests Roche had conducted, both clinically and in the lab, Böhni argued that the combination improved efficacy, and resistance developed more slowly, which was why trimethoprim was licensed in the US in combination only. In her report on the threatened solo development of trimethoprim, the Bactrim pioneer came to the conclusion: ‘We will destroy the approach we’ve painstakingly developed over the last 12 years (even if Welcome acts alone) and with it all promising future combinations of this nature.’

In fact, it proved impossible to prevent the emergence of single-agent trimethoprim (Infectotrimet); and some researchers even credited it with superior tolerability since it managed without a sulfonamide.

Research also continued on other combinations, but Roche came to the conclusion that sulfamoxole was substantially inferior to the conventional sulfamethoxazole in its antibacterial qualities, even in combination with trimethoprim.197 In the constant search for a successor product, trimethoprim and sulfadiazine were combined in a ratio of one to three (Ro 12-2510). Studies were conducted on *in vitro* and *in vivo* activity, pharmacological and pharmacokinetic properties, adverse effects, animal toxicology and, lastly, the clinical use of this combination. Sulfadiazine was found to diffuse astonishingly well into bronchial tissue, bronchial secretions and saliva, which promised good chemotherapeutic effect in respiratory tract infections.198

At the 10th International Congress of Chemotherapy from 18 to 23 September 1977, some 3000 scientists met in Zurich; more than 60 papers were given on Roche products, many of them on Bactrim.199 In 1981, John Marks, a doctor and Head of Roche London, and the Basel microbiologist and Roche researcher Pierre Reusser published a comprehensive monograph on Bactrim.200 Drawing on the latest scientific findings, they reviewed the ideas and evidence behind the drug, along with information on its clinical use, adverse effects and specific product characteristics. Whereas the literature list in the launch brochure of 1969 contained 51 references201; that figure had now mushroomed to 941.202

Bactrim sales peaked at 441 million Swiss francs in 1985, 16 years after launch and the year Valium, Roche’s biggest earner, went off patent. Increased use of the medicine against bacterial infections in the acquired immune deficiency syndrome (AIDS) setting undoubtedly contributed to Bactrim’s success as well. The World Health Organization (WHO) continues to recommend cotrimoxazole (including Bactrim) as a simple, well-tolerated and cheap method of preventing secondary infections in adult and pediatric HIV patients in third-world countries.203 This pragmatic measure on the part of the UN AIDS programme costs eight dollars per head per treatment cycle. By contrast, conventional antiviral combination therapy in the West cost about 15,000 dollars per month in 2000. This WHO-sponsored recommendation, however, was regarded by some as discriminatory and therefore met with sharp criticism.204

Apart from a slight slump in 1978, Bactrim sales had risen steadily and in 1981 exceeded the 400 million mark. Due to patent expiries after 1989 and an increasing number of generics, Bactrim sales have stayed below 100 million Swiss francs since 2008.205 Roche and Wellcome had to contend with dangerous counterfeit products in 1982 in Germany and the Lebanon.206 In 1988, George L Drusano, a pharmacologist at the Albany Medical College in New York, compiled a book entitled *Bactrim today.*207 Numerous

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189 *[Combination trimethoprim + sulfadiazine (1 + 5) Ro 12-2510: Description for clinical use].* RHA FE.2.1 – 103531 a.
190 Sechting Referate über Roche Chemotherapeutika (Listy papers on Roche chemotherapeutic agents). Roche Nachrichten, December issue, 5/1972, 14.
197 Bactrim sales 1969-2010. RHA FR.2.3.5 – 107395.
199 http://www.roche.com/de/corporate_responsibility/patients/access_to_healthcare/developing_countries/what_essential_medicines.htm
201 http://www.roche.com/de/corporate_responsibility/patients/access_to_healthcare/developing_countries/what_essential_medicines.htm
202 Bactrim sales 1969-2010. RHA FR.2.3.5 – 107395.
205 Bactrim sales 1969-2010. RHA FR.2.3.5 – 107395.
impressive graphs show the efficacy rates achieved by Bactrim shortly before it went off patent. However, no dry treatment statistics and certainly no sales curves can depict for us the effect that Bactrim has had on the many hundreds of millions of patients of all ages who have been treated with it. Each individual treatment success in infants, children, adolescents, adults and the elderly is an enormous relief for both patient and family, whether in an Indian metropolis, the middle of an African rainforest or on an isolated Canadian farm. For developing countries in particular, Bactrim provides a significant advance in the treatment of everyday but often life-threatening diseases.

**Expiry of patent protection**

Following patent expiry, competition intensified as expected. Numerous generics were launched at up to 50% off. For example, in 1994 twenty tablets of the generic Goprim cost less than 11 Swiss francs, as opposed to more than 20 Swiss francs for the original product. In the mid-1990s a pack of Bactrim in Switzerland was supplied to pharmacists for 15 Swiss francs and was sold for 20 Swiss francs. In France the same pack cost 22 French francs, almost four times less. Certainly Roche could argue exchange rate differentials, but at launch the product cost the same in both countries. When the Federal Social Insurance Office set the price for medicines reimbursed under the compulsory health insurance scheme, Bactrim was significantly cheaper after 2000. The price today in all markets is about half that of the cheapest conventional antibiotics. The 480 mg tablet of cotrimoxazole (400 mg sulfamethoxazole + 80 mg trimethoprim), for example, is supplied in India for 42 cents and in Thailand for just under a dollar. And the price actually paid is often even lower; special offers at 14 cents a tablet are not uncommon. Moreover, national health services and relief organisations buy directly from the manufacturers and consequently obtain a large discount.

On 27 February 1994, England’s *Sunday Times* ran a headline story levelling serious accusations at Bactrim/Septrin. Since 1969, the paper said, the medicine had officially caused 113 deaths in Great Britain and the number of unreported cases was no doubt far higher. Roche did not dispute the official death toll, but did question the plausibility of a high number of unreported deaths given Britain’s excellent reporting system for adverse events. The number of tragic deaths was also contrasted with the five million patients cured in Great Britain alone. Alongside such negative headlines, there are good news items that should not be forgotten: following the tsunami flood disaster at the end of 2004 in eight Asian countries, Roche donated 220,000 packs of Bactrim and Rocephin, worth a million Swiss francs, to ‘Swiss Solidarity’ for the urgently needed medical care of 80,000 survivors.

Certainly the euphoric belief in the 1970s and early 1980s that vaccination and medication could eliminate the scourge of infection has now dissipated. In the case of bacterial infections in particular, increasing allowance must be made for the worrying development of resistance and reduced immunity. Unrestricted cross-border mobility and tourism, but also natural disasters, war, hunger and poverty, have had the unwanted side effect of spreading known micro-organisms and engendering new ones and, with them, the development of new diseases. Here too Bactrim is meeting its match: almost 25% of isolates of the urinary tract pathogen *Escherichia coli* are no longer susceptible.

Despite such worrying developments, the Bactrim story remains one of a medicine with an impressive bacterical effect, outstanding therapeutic efficacy, relatively minor resistance even now and good tolerability. Many hundreds of millions of people on every continent owe their lives to cotrimoxazole. Bactrim no longer stands alone, but shares the market with many generics, some of which are available at extremely low prices.

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208 Why cheap products, when there are expensive ones? [Cash, 20 August 1993]
209 1000 drugs are becoming dramatically cheaper. [Cash, 14 June 1996]
210 1000 Medicamente werden massiv billiger
211 Medikamente sind (fast) nie harmlos.
212 Flutwelle. Der grosse Sammeltag. Nach der
213 1000 Mediamente werden massiv billiger
214 Prof. Dr. Terapong Tantawichien, Head of Infectious Diseases Unit, Chulalongkom University and Medical School, 21 July 2011.
treatment of bacterial infections would not be possible in most countries today. As a result of the major scientific and financial efforts invested by both companies, a wide variety of different dosage forms for all age groups and types of disease is also available to the world, as well as confirmed product data. Following patent expiry, all this is now in the public domain and can be used by anyone free of charge.

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The discovery of cephalosporins

In 1945 Giuseppe Brotzu was studying seawater samples taken from the direct vicinity of a sewage outfall off the Sardinian coast. He suspected that the observed ability of the seawater to detoxify itself could partly be attributed to the fact that microorganisms attacked and destroyed one another using endogenous antitoxins. He isolated the fungus *Cephalosporium acremonium* from the water samples and discovered that it produced and released metabolites with antibiotic activity that were effective against a whole range of pathogens. Brotzu prepared large cultures of the fungus and sought to extract these ‘antibiotics’ in sufficient amounts: his aim was to trial them in clinical experiments and elucidate their structure. The first part of this project was successful: he injected his concentrates into patients with various kinds of infection and a good number recovered. Brotzu had discovered the first of a new class of antibiotics later called ‘cephalosporins’, after the original fungus.

Brotzu failed in the second part of his project. Given his limited resources he was unable to isolate the antibiotic ingredient in a pure enough form for structural studies. However, in 1948 he made contact with penicillin researchers in Oxford who enthusiastically took up the task of producing, isolating and elucidating the structure of the antibiotic component in *C. acremonium*. In 1954 two of these researchers (E. P. Abraham and G. G. F. Newton) isolated two components of the fungus – penicillin N (with the chemical skeleton of penicillin) and cephalosporin C, a substance that proved to have extremely interesting properties. In contrast to penicillin N, cephalosporin C was acid-resistant and resistant to the penicillinase enzyme, a weapon produced by certain bacteria that cleaves the beta-lactam ring and inactivates penicillin. Penicillinase-mediated resistance was responsible for a growing number of infectious disease patients responding inadequately or not at all to penicillin treatment. Certain bacteria had become resistant to the classic antibiotic. X-ray structural analyses showed that the cephalosporin C skeleton consisted of a beta-lactam dihydrothiazine ring system. The fact that the side chain on the molecular skeleton appeared identical to that of penicillin N prompted the following conclusion: the valuable ability of cephalosporin C to resist bacterial penicillinase was grounded not in the side chain but in the beta-lactam ring system. Scientists immediately set about synthesising the cephalosporin core and experimentally modifying it in order to produce cephalosporins capable of combating infectious diseases more effectively than ever before.

This was the starting gun for worldwide cephalosporin research. It had a decisive impact on the strategy of most research-driven drug companies in the 1960s, 1970s and into the mid-1980s. The cephalosporin skeleton proved an extraordinarily fruitful substrate for chemical modifications, resulting in the discovery of countless safe and effective cephalosporins.

Antibacterial activity

The term ‘antibiotic’ is derived from the Latin ‘anti’ (against) and Greek ‘bios’ (life). All chemical substances that inhibit microbial growth *in vitro* (in the laboratory) and *in vivo* (in the organism) are termed antibiotics; an equivalent term, anti-infective (or anti-infective agent), is often used today as the ‘against life’ translation of ‘antibiotic’ could convey the wrong message for those with no scientific background.

Available antibiotics differ in many respects. Mode of action and, more particularly, spectrum of activity are the most relevant for prescribers and patients, along of course with possible adverse drug reactions. They also differ in origin, chemical composition and type of resistance development. Cephalosporins and penicillins make up the beta-lactam antibiotic ‘family’. Their common feature is their beta-lactam ring: it is attached in cephalosporins to a dihydrothiazine ring (giving...
Cephalosporin research

The aim of the cephalosporin research that took off worldwide in the early 1960s and soon reached a fever pitch was to optimise efficacy and tolerance by chemically modifying the side chains of 7-cephalosporanic acid. The prospects of a huge market provided a powerful incentive for the research groups involved.

What got Roche’s cephalosporin programme going in 1969 was the realisation that, while the company enjoyed a strong position amongst general practitioners (thanks to sulphonamides and Bactrim), it was scarcely present at all in the hospital market. Roche’s chemical and medical departments therefore decided to set up a programme to synthesise semisynthetic penicillins, and at a later stage cephalosporins too. At that time many of its rivals already had a successful track record in this sector and access for new companies was considerably impeded by the existing patents, some of which had a very broad scope. Furthermore, the research groups at Roche were smaller than those of its rivals.

The synthesis and development of Rocephin can be attributed to the exceptional commitment and team work of chemists, pharmacologists, microbiologists, toxicologists, formulation scientists, pharmacokineticists, process engineers, clinicians and marketing specialists.

In the initial years chemist Roland Reiner, microbiologist Peter Angehrn and biologist Peter Probst, together with their staff, were the main driving force. In a letter dated 1 November 2010 Peter Angehrn recalled:

‘As a rule it is the fascinating interaction between diverse factors and people at the right time in the right place that leads to successful discoveries. You also have to have luck on your side. That’s what happened with Rocephin.’

When Roland Reiner began his mission in 1969 of taking a critical look at cephalosporins, he faced a basic problem: the core structure (7-cephalosporanic acid) could not be purchased from any fine chemicals supplier. Reiner therefore had to isolate this substance from an already commercially available cephalosporin by cleaving off its side chain. There was, however, a major drawback: the antibiotic that he needed in 100 g batches for his work

7-aminocephalosporanic acid) and in penicillins to a thiazolidine ring (giving 6-aminopenicillanic acid).

Besides this structural relationship beta-lactam antibiotics also have a common mode of action: they achieve their bactericidal (‘bacteria-killing’) effect against susceptible organisms by inhibiting cell wall synthesis. Their main target is the murein (or peptidoglycan) skeleton, a glycoprotein polymer responsible for the structural strength of bacteria. Both cephalosporins and penicillins bind to enzymes involved in building the murein skeleton. Because the resulting cell wall is incompletely synthesised it is unable to protect the bacterium from the force of osmotic pressure; the bacterium bursts and dies. Thus beta-lactam antibiotics are only effective against replicating bacteria; they do not kill resting bacteria.

Antibiotic resistance

Bacterial resistance to antibiotics remains a highly topical problem involving almost all antibiotics and pathogens.

In terms of clinical use resistance means that an antibiotic fails to achieve the minimum concentration at the focus of infection required to destroy or inhibit pathogen growth (bactericidal or bacteriostatic effect, respectively). Besides the well-known phenomenon of natural resistance, there is also acquired resistance, which plays a far more important role. Acquired resistance stems from chromosome mutation or the transfer of genetic material.

Resistance acquired through mutation is an infrequent occurrence and only takes on clinical importance under selection pressure, i.e. in conjunction with the prolonged administration of the antibiotic that causes resistance. Switching and/or combining antibiotics can prevent the development of such resistance.

Resistance acquired through transfer accounts for 90% of clinically relevant antibiotic resistance. Various complex mechanisms may be involved in the transfer of genetic material containing the resistance properties.
ambitious project of synthesising an innovative new cephalosporin. In the end it was management’s faith in the research and development teams that made the difference. Critical – and frustrating – as the situation was, the teams were encouraged to keep going, and the work atmosphere was hearteningly creative. The sometimes scathing assessments by internal and external experts were not taken too seriously because both the researchers and their superiors believed in what they were doing.

Between 1969 and 1977 Roche synthesised and tested over 400 cephalosporin derivatives, although not all in the same detail. It proved very helpful for Reiner’s laboratory to receive a constant stream of intermediaries from the research team of Marc Montavon, who was head of chemical research and had initiated the research programme on cephalosporanic acid. However, no compound performed convincingly in all three target properties: broad antibacterial spectrum, resistance to known beta-lactamases (enzymes produced by some bacteria that cleave the ring structure of beta-lactam antibiotics) and the longest possible retention time in patients.

The complex patent situation also threw up major hurdles. There was hardly a drug company that was not active in the cephalosporin field: many products had already been introduced and patents held by the leading companies protected most of the relevant chemical compounds.

The first compounds that Roland Reiner synthesised with his laboratory head, Urs Weiss, did not even come close to meeting the requirements of the broad antibacterial activity spectrum desired. The decisive factor on the biological side was that – contrary to usual practice – pharmacokinetic screening had also been included in the antibacterial characterisation of the test substances. This was not standard practice in this field and had little by way of rational justification, in particular as experts thought it unlikely that a penicillin or cephalosporin could have a long retention time in the body.

Proceeding stepwise, Peter Angehrn first screened several hundred candidate substances in vitro and in vivo, identifying several dozen that looked interesting enough in terms of their activity to merit pharmacokinetic testing by Peter Probst in relatively comprehensive studies in rats and rabbits. A good pharmacokinetic profile was not, of course, the precondition for a substance to be further developed: several candidates proceeded to further development because of their excellent antibacterial properties despite having an unpromising pharmacokinetic profile. But ultimately they revealed weaknesses compared to rival candidates and were dropped.

During this period (1969–1977) there were voices inside and outside Roche arguing that the company should abandon its could only be purchased from a pharmacy and it was expensive. Each order cost thousands of Swiss francs. Reiner recollected:

‘I was very anxious every time until the next approval came through. As prospects were extremely uncertain, research management understandably developed concerns as time went by. Sometimes I had to call on all my powers of persuasion. Fortunately, these were considerable as I was convinced of being able to find the right substance.’
Discovery of Rocephin

In the final days of 1977 Roland Reiner and Urs Weiss discovered an as yet unpurified active ingredient which was given the name ceftriaxone in August 1980 by the World Health Organisation. Its Roche code name was Ro 13-9904. Roland Reiner recalled:

‘To obtain a product with the requisite purity, it was imperative for us to produce it in crystals. But cephalosporins don’t really like to crystallize. My laboratory head and I tussled with this problem for many days.’

Four weeks later they managed it: on 26 January 1978 3.5 g of a beige coarse-grained powder collected on the bottom of a laboratory flask: Rocephin was born!

Ro 13-9904 was the very first test substance synthesised at Roche as a third-generation cephalosporin after Hoechst-Roussel launched this substance class with cefotaxime and revealed the epoch-making invention in a 1977 publication. Peter Angehrn and his team observed unusually potent and wide-ranging antibacterial activity by Ro 13-9904: in the three animal models (mouse, rat, rabbit) studied together with Peter Probst, the compound revealed unexpectedly marked effects on various experimental infections, far exceeding those that could be explained by resistance studies on nutrient medium. The research team took this to indicate that they had found the compound with the long retention time that they had sought for so many years. Various pharmacokinetic studies – in particular in rabbits – confirmed the unusually long retention of Ro 13-9904. Blood samples taken several hours after injection also demonstrated major bactericidal effects on nutrient medium, most probably due to the unchanged substance, as indicated by various experimental designs.

Just five months after beginning their experiments Peter Angehrn and Peter Probst summed up their observations in an internal research report dated 19 June 1978:

‘The results show remarkable efficacy by Ro 13-9904 in vitro and in vivo. Its activity markedly exceeds that of other substances against the majority of bacterial strains tested, with particular respect to the feared and notoriously resistant strains of Pseudomonas aeruginosa. Ro 13-9904 achieved high and sustained levels of antibacterial activity in rabbit plasma after intramuscular injection... Based on these favourable findings, we suggest starting preparations for a preliminary clinical trial of Ro 13-9904 and pushing quickly ahead with a view to speedy development in the cephalosporin sector’.

Internal research report by Peter Angehrn and Peter Probst containing the first official description of their observations.
‘Discussing the place of cephalosporins in pediatrics is a difficult and delicate task. The large number of cephalosporin antibiotics currently available, the innumerable scientific publications, personal experience and the flood of advertising copy impede the sound, objective and unimpassioned assessment of these drugs for daily pediatric practice in surgeries and hospitals.’ And he continued: ‘The results of two recent surveys (1981) among Swiss physicians revealed that most respondents have reservations about the indications for cephalosporins. Around three-quarters view them as second-line antibiotics that should largely be reserved for the hospital setting.’

Introduction of Rocephin

In July 1978 research management gave the green light for further development of Ro 13-9904. The laboratories of chemists Andreas Furlenmeier and Rudolf Hug channelled every possible effort into synthesising kilogram amounts of the new cephalosporin within the shortest possible time.

Animal toxicology was tested in rats and dogs. The findings in dogs were unsettling: toxicologist Karl Schärer observed that Ro 13-9904 produced centimetre-sized gallstones. The substance seemed doomed to an early demise. This was perhaps the most critical moment in the development phase. No-one could have criticised Schärer at this point for deeming the toxicological risk too great for tests in humans. But he and all the other researchers involved wanted to press on. Using an ingenious dosage regimen, Schärer conducted an additional trial in monkeys. His aim was to show that the gallstone problem was primarily specific to dogs – and he succeeded. Precipitates were subsequently also observed in conjunction with Rocephin in humans but they fortunately proved harmless in almost all cases.

As no further toxicological or other problems arose during preparations for clinical trials and production on the kilogram scale was proceeding satisfactorily, the first human trials were launched in May 1979. Initially it was unclear whether and how the favourable pharmacokinetic profile would transfer from animals to humans. The observed plasma half-life of 6–8 hours and hepatorenal excretion were optimal, enabling Rocephin to be administered by once-daily intravenous injection in contrast to all other beta-lactam antibiotics.

The clinical trial was headed by the experienced Michel Fernex, who had been convinced of the potential of Ro 13-9904 from the very outset. Together with his assistant, Ladislaus Havas, he showed incredible dynamism by taking Ro 13-9904 through clinical development in a record three years, enabling it to be launched on 27 May 1982 in Switzerland under the brand name Rocephin. Its path from initial synthesis in the laboratory to market launch had taken less than five years.

Most doctors were sceptical about the new cephalosporin. The author of this chapter (Urs B. Schaad) wrote in 1983 in a further training series for pediatricians:
Ro 13-9904 was launched under the brand Rocephin in Switzerland already on the 27th of May 1982.

Even Roche Marketing was somewhat negative about the introduction of Rocephin. For instance, there was the difficult patent situation which meant that Roche had to continue paying substantial royalties to other companies. Industrial-scale technical synthesis was still considered too expensive. Furthermore, Marketing saw no significant advantage in ‘once-daily administration’. These reservations prompted sales projections of only 40–60 million Swiss francs with an achievable market share of 2–4% three years after launch. The Roche decision-making bodies did not share Marketing’s opinion but backed the arguments of the Rocephin team.

Pharmacokineticist Klaus Stoeckel and his American colleagues in Nutley were also major contributors to the success of Rocephin. In publications and multiple presentations, Stoeckel made an expert and highly impressive scientific case for the unique pharmacokinetic profile of Rocephin, enabling him to overcome doctors’ reservations. Together with Klaus Stoeckel, I obtained and published the pharmacokinetic data for Rocephin in infants and neonates, confirming that the drug’s favourable pharmacokinetic profile – in particular, its unusually long elimination half-life of 6–7 hours – applied to these age groups too.

Roche staff in Nutley under Roy Cleeland did splendid work in preparing North American infectiologists for the introduction of Rocephin that was later to prove so successful. During my research stay in Dallas he was the first to test Rocephin in the rabbit meningitis model and he showed how effective it was against both Escherichia coli and beta-streptococci.

The results of clinical studies in many countries confirmed that Rocephin was a highly suitable drug for treating many bacterial infections. The most important indications tested were sepsis (blood poisoning) and meningitis, bone and soft tissue (including wound) infections, and infections of the airways, kidneys and urinary tract, including sexually transmitted diseases. Another key indication was perioperative prophylaxis.

Within a few years, innovative, highly potent once-daily Rocephin became the world’s number one injectable antibiotic. This unique drug secured a lasting reputation for Roche and generated billions in sales before patent expiry.
Special aspects of Rocephin

Structure of Rocephin

Rocephin is a semisynthetic cephalosporin that was discovered in the Roche programme from 1969 to 1978 designed to identify an innovative cephalosporin exhibiting broad-spectrum activity, beta-lactamase resistance and a long elimination half-life.

The side chain to 7-aminocephalosporanic acid on the right of the structure differs fundamentally from that of other cephalosporins and is responsible for most of the unusual antibacterial and pharmacokinetic properties of Rocephin.

Antibacterial efficacy

The antibacterial properties of Rocephin include a broad spectrum of activity and beta-lactamase stability.

The impressive Gram-negative spectrum covers in particular the Enterobacteriaceae (E. coli, Klebsiella sp., Enterobacter sp., Serratia sp., Bartonella sp., Citrobacter sp., Proteus, Salmonella, Shigella, and to some extent Pseudomonas aeruginosa and Acinetobacter sp.), various Haemophilus (beta-lactamase-negative and -positive strains) and Neisseria (N. meningitidis and N. gonorrhoeae).

The main Gram-positive pathogens susceptible to Rocephin are Streptococcus pneumoniae, S. pyogenes and S. agalactiae and, to a lesser degree, Staphylococcus aureus.

Rocephin efficacy is limited against anaerobes and non-existent against Mycoplasma, Ureaplasma and Mycobacteria. At launch, Rocephin was stable against most of the beta-lactamases then known to inactivate cephalosporins.

Such broad and potent antibacterial efficacy gives Rocephin the following two major advantages in clinical use:

1. Rocephin is suitable for the treatment of the most serious invasive infectious diseases such as meningitis and sepsis (blood poisoning) and acute infections in almost all organ systems.

Antibiotic treatment markedly improved the prognosis for the much feared purulent meningitis. This became the most important indication for Rocephin and has remained so for the past three decades worldwide.

The most important bacterial meningitis pathogens during childhood and adulthood are meningococci, pneumococci and H. influenzae. H. influenzae type B has almost disappeared in industrialised countries thanks to the active vaccination given to infants but has yet to be eradicated in the many developing countries that cannot afford vaccination. Despite all the progress made – particularly in improved early diagnosis, specialised intensive care and effective antibiotics – the prognosis for purulent meningitis remains grim.

“Few diseases have been affected more by the advent of antimicrobial therapy than bacterial meningitis.”

Quagliarello VJ, Scheld WM. N Engl J Med 1997; 336:708

Septic newborn

Septic infant

Septic shock with multiple organ failure.
meningitis remains guarded. Depending on patient age, pathogen and the timeliness and quality of care and treatment, mortality is 3–30%, with sequelae in 10–50%.

2 Rocephin also has the requisite antibacterial properties for initiating ‘blind’ therapy, i.e. when the pathogen is still unknown, or serious invasive infection is suspected.

Only a few years after the launch of Rocephin, extended spectrum beta-lactamases (ESBL) were identified. These were enzymes produced by various *Enterobacteriaceae* (in particular *Klebsiella* sp. and *Serratia* sp.) capable of inactivating all the beta-lactam antibiotics known at the time. Individual case reports were soon followed by hospital outbreaks, first in France, then in the USA and later in many other countries. Even carbapenems – the new class of beta-lactam antibiotics introduced from around 1985 onwards – fared no better: some intestinal bacteria were able to take up and transfer genetic material that produced carbapenemases (beta-lactamases capable of hydrolysing carbapenems). Moreover, the development of such resistance led to the appearance of the extensively drug-resistant (XDR) bacteria first discovered in New Delhi in 2008 that were non-susceptible to almost all other antibiotic classes.

Unfortunately, such multiresistant *Enterobacteriaceae* were introduced into many other countries with corresponding clinical consequences, fortunately mostly only in isolated cases or mini-outbreaks. The development of such extremely disquieting and threatening global resistance led to cross-border epidemiological registries and harmonised recommendations for diagnosis, prevention and management.

### Pharmacokinetics

The high affinity of Rocephin/ceftriaxone for serum albumin accounts for its distinctive distribution and elimination kinetics. Protein binding is not only more marked, it is also more concentration-dependent than that of other cephalosporins.

The extremely long elimination half-life is due to an absence of tubular secretion and relatively low glomerular filtration; the latter in particular can be attributed to the high level of serum albumin binding. Quantitatively significant biliary excretion (around one-third of the total) makes the rate of elimination less dependent on kidney function. Consequently, dose adjustment is only necessary in severe renal failure. The high level of concentration-dependent
protein binding also plays an important role in maintaining elevated Rocephin levels in body fluids and tissues.

The fact that the unbound (free) Rocephin fraction has antibacterial activity implies ‘high’ administration doses, which is an advantage in view of the wide therapeutic range.

Rocephin is not metabolised, meaning that there is little likelihood of drug-drug interactions such as competitive elimination inhibition or enzyme induction. Nor is there competitive inhibition of tubular secretion, in contrast to many other beta-lactam antibiotics. The high affinity for serum albumin has the potential to suppress other similarly highly protein-bound metabolites or drugs. This needs to be taken into account in very rare situations (for instance, the suppression of bilirubin in jaundice, particularly in neonates).

These distinctive pharmacokinetic properties account for the following four additional major advantages:

### 1. Generation
- Cefazolin Renal 78–82% in 24 hrs
- Cefalotin Renal 78% in 6 hrs
- Cefazolin Renal 73% in 6 hrs
- Desacetylcefalotin (35%)
- Desacetylcefapirin

### 2. Generation
- Cefamandol Renal 65–85% in 8 hrs
- Cefonicid Renal 58% in 6 hrs
- Cefoxitin Renal 85% in 6 hrs
- Cefuroxim Renal 89% in 8 hrs
- Desacetylcefoperazon

### 3. Generation
- Cefmenoxim Renal 81–88% in 24 hrs
- Cefoperazon Renal, biliary 20–30% in 24 hrs
- Cefotaxim Renal 78–80%
- Desacetylcefotaxim (15–25%) U1 and U2 (20–25%)
- Ceftriaxon Renal, biliary 33–67% Through colonic flora inactivated metabolite after biliary excretion

3 Thanks to its long elimination half-life Rocephin can be administered once daily, meaning that parenteral antibiotic therapy can be given on an ambulatory basis early on or even from the very start of treatment. This has a favourable impact on the patient, the family and costs. Intramuscular administration is a viable option, not only for outpatient management but also for hospitalised patients with difficult venous access, for instance infants, the obese and the elderly. After intramuscular administration the pharmacokinetic profile is similar in terms of distribution and elimination kinetics to that after intravenous administration. Local tolerance is also good. Thanks to the rapid and complete systemic availability of Rocephin, plasma levels two hours after intramuscular administration are as high as after intravenous administration.
The long retention time of high levels at the site of infection accounts for the excellent clinical response to the active ingredient even from infectious diseases caused by bacteria that are only moderately susceptible in vitro.

As the body does not metabolise Rocephin, the entire administered dose continues to exert antibacterial activity until the moment of excretion.

The fact that Rocephin is excreted via the kidneys (urine) and liver (bile) – with one organ being able to compensate for the failure of the other – means that the dose only has to be adjusted in massive renal and/or hepatic impairment.

**Toxicity and adverse drug reactions**

Rocephin underwent extensive toxicity testing in rodents, rabbits, dogs and monkeys. It proved safe in terms of acute and subacute toxicity, fetotoxicity, mutagenicity and local tolerance.

Intravenous Rocephin is very well tolerated and patients have very rarely complained of transient post-injection pain. Dissolution in 1% lidocaine solution is effective in intramuscular administration. Hence local tolerability may be described as unproblematic.

Systemic tolerability matches the good results seen with other beta-lactam antibiotics, with the additional advantages of virtually no effect on renal function and extremely rare interaction with other drugs and alcohol. Serious drug reactions are also very rare and include, besides anaphylaxis, potential biliary or renal (calcium salt) lithiasis, hemolysis (drug-induced immune-mediated destruction of red blood cells) and displacement of bilirubin from albumin binding, which is of potential significance in jaundice, in particular in neonates.

Non-toxicity and excellent local and systemic tolerability are further major advantages of Rocephin.

The seven major advantages of Rocephin listed in Table 1 account for its sustained clinical benefit and cost-effectiveness.

**Clinical use**

The incomparably broad spectrum of indications derives from the two antibacterial advantages of Rocephin (treatment of the most serious infectious diseases and initiation of blind therapy), allied to its pharmacokinetically elucidated properties of marked clinical efficacy, even against bacteria that are only moderately susceptible in vitro, negligible metabolism and extremely rare interaction with other drugs and alcohol. The most important indications for Rocephin are serious and/or invasive infectious diseases, most of which are blood-

![Lower lobe infiltrate (bacterial pneumonia)](image-url)
borne (hematogenic), meaning that the bacteria are carried to the site of infection in the bloodstream. Besides actual sepsis (blood poisoning), this group includes most forms of meningitis and some infections of the lung, bone, abdomen and other organs. Rocephin can also eliminate many non-hematogenic bacterial infections in the abdomen, kidneys and urinary tract, bone, soft tissue and skin, and upper and lower airways, including ear, nose and throat. Special mention should be made of perioperative infection prophylaxis and treatment, infections in immunocompromised patients and neuroborreliosis (Lyme’s disease), along with selected presentations of otitis media.

The breadth of this spectrum, to which virtually no other antibiotic comes close, is thus based on broad therapeutic efficacy and an excellent safety and tolerability profile. For patients, doctors and healthcare workers, Rocephin has represented sustained medical benefit that continues to this day.

**Economic benefits**

The advantages of once-daily administration, negligible metabolism, and hepatorenal elimination are primarily responsible for the clinical savings (in supervision, supplies, nursing staff and time) and for the laboratory savings (hepatorenal monitoring), as well as for shorter hospital stay and lower drug costs. The following detailed exposition of the long-term impact of Rocephin on healthcare costs draws on examples published shortly after the drug’s introduction.

Between 1979 and 1981, 127 adults at the Centre Hospitalier Universitaire Vaudois (CHUV) in Lausanne, Switzerland, received Rocephin for a total of 132 serious mostly bacteremic infections caused by Gram-negative intestinal bacteria; 80 infections had previously been treated with other antibiotics without success. In 65 infections Rocephin was administered twice daily and in 67 infections once daily; the high overall response rate – 86% – and excellent tolerability were the same in both groups. A comprehensive and detailed cost breakdown pinpointed major savings with Rocephin. Compared to the conventional antibiotic regimen of four doses daily, once-daily Rocephin achieved cost savings of CHF 31.38 per day in terms of nursing care and materials (needles, syringes, sterile fluids for intravenous antibiotic dissolution and administration). This amounted to the saving of CHF 658.98 per patient hospitalised for the 21 days standard at the time. Rocephin drug costs were similar to those of conventional antibiotics. Twenty-five patients were able to be treated on an ambulatory basis; at that time staff and material costs per domiciliary Rocephin injection cost an estimated CHF 40. In 1981 the average cost of an inpatient day at the CHUV was CHF 460, meaning that each ambulatory treatment saved CHF 420 per day. These costs have since risen 3- to 4-fold in Switzerland, as have also, of course, the savings.

In 1986 results were reported from St Michaels Medical Center, Newark NJ, in 38 patients with serious systemic infections (osteomyelitis: n=20; cellulitis: n=4) who were treated with Rocephin. Clinical response, bacteriological eradication, healing and tolerability were excellent. The most important and relevant cost saving was the 60% shortening of hospital stay. The hospital was already using the Medicare diagnosis-related group (DRG) system to calculate most patients’ costs.

In 1986 Russel Steele (Arkansas) identified the relevant clinical and cost advantages of Rocephin therapy in pediatric patients. The key clinical advantages were potent and broad antibacterial activity, beta-lactamase resistance, excellent penetration into cerebrospinal fluid and virtual absence of toxicity. Steele detailed the economic advantages as savings in drugs (reduced overall requirement), administration (supplies, nursing care) and laboratory monitoring (determination of drug levels). The relevant economic advantages were calculated for both inpatient and outpatient treatment.

In 1984/1985 the Saint Vincent Medical Center in Toledo, Ohio, examined the feasibility of an early switch from inpatient to outpatient treatment in 98 adults with serious bacterial infections (bone: n=24, skin/soft tissue: n=22, abdomen: n=17, lung: n=16, blood vessels: n=12, kidney: n=4, meningitis: n=1, endometritis: n=1). Clinical and bacteriological response to once-daily intravenous Rocephin 2 g was excellent overall in 96% (resolution: n=82, improvement: n=13). Treatment was well tolerated, with adverse reactions in only 13 patients (diarrhea: n=8; skin rash: n=4; abdominal cramps: n=1). Patients were switched individually from inpatient to outpatient care according to standardised improvement criteria. Of a total 1956 treatment days in the 98 patients (average treatment duration: 20 days), 924 (47.2%) took place after discharge from hospital, saving nearly 0.5 million dollars.
Its broad and distinctive antibacterial spectrum, unique and remarkable pharmacokinetic properties and advantageous safety and tolerability profile account for the drug’s considerable advantages in terms of sustained clinical and cost benefits. Rocephin simplifies the successful treatment of infectious diseases while reducing healthcare costs. These advantages continue to benefit both industrialised and developing countries, even after patent expiry.

**Patent expiry**

Between 1997 and 2005, the company met the challenge of Rocephin patent expiry around the globe. As the world’s most prescribed injectable antibiotic, Rocephin had become Roche’s top-selling drug. Generic production of ceftriaxone was therefore an extremely attractive venture and products mushroomed. By the end of 1999, 2012 different ceftriaxone generics were on the market, produced in 38 different countries, mostly in Asia, followed by South/Central America and Eastern Europe.


A special expert group at Roche, the Post-Patent Strategy Task Force, analysed the situation and developed strategies to maintain as high a share of the ceftriaxone global market as possible. With the arrival of the generics they anticipated expansion of the market driven by the attractiveness of ceftriaxone as an antibiotic, lower prices and a relaxation of prescribing restrictions. The Task Force looked at sales figures, prices, production and distribution as well as standard costs for proprietary products, such as the costs of research and scientific information which did not apply to generics.

They estimated that the global market would expand to 300 tonnes of ceftriaxone in 2010, or double that in 1997 (150 tonnes): the most important drivers were the factors already mentioned, such as price erosion (estimated at 60–70%) and broader indications (relaxation of prescribing restrictions). In addition there was the pressure on clinicians from those responsible for healthcare costs to make more use of this unique and now much cheaper drug. Restrictive recommendations from expert bodies were cited as a factor that might ‘contain’ market expansion. Another factor taken into consideration was that patients might be switched from Rocephin to newly approved and actively promoted antibiotics.

Regarding the production and marketing of ceftriaxone generics, the Task Force noted a major lack of clarity in responsibilities for production of the raw material, packaging and delivery of the injection vials. It was also clear that countless suppliers did not adhere to price lists or discount conventions: hospitals, the main buyers, were the target of every conceivable marketing trick.
On Task Force recommendation, Roche developed a standardised analytical method for the objective examination of the production and packaging of ceftriaxone generics. Different quality factors were examined: appearance and purity of the ceftriaxone powder (in particular neither lumpy nor granular), colour (ideally off-white), purity of the injection solution (clear and particle-free) and various chemical tests (raw material purity, solution clouding, water quality, absence of solvents). More than 20 generics from eight different countries underwent these analyses and were compared with proprietary Rocephin. The results failed to reveal major deviations between the generics and Rocephin, thus ruling out legal action to stem the proliferation of generics. The ceftriaxone generics examined by Roche had all been procured as approved drugs in the respective countries; a conscious decision was taken to refrain from analysing me-too drugs from dubious sources.

In addition to standardised analysis at Roche headquarters in Basel, Roche subsidiaries in several countries, above all China, also compared the packaging of the generics with that of Rocephin. In many cases the quality of the boxes, card paper and labelling, like that of the injection vials, glass, sealing and labelling, reflected the cost-cutting measures used in generics manufacture and thus exhibited clear shortcomings in comparison with the proprietary product.

Competing with generics

During the final years of the 20th century Roche increasingly lost control over one of the biggest products in pharmaceutical history. Rocephin accounted for over 10% of Roche sales at the time. With utmost care and commitment the Task Force collected all conceivable data and facts about the generics and fed them into a central database. At the end of 1999 the database contained information on 132 generics from Asia, 95 from Latin America and 30 from Eastern Europe.

To ensure the strongest possible position for Rocephin versus the generics in the various countries, the Task Force conducted comprehensive comparative analyses of their strengths, weaknesses, opportunities and threats (SWOT). It then reviewed the theoretical conclusions for each national subsidiary individually and developed an appropriate strategy. The most important conclusions from these SWOT ANALYSES are summarised below.

Strengths

The predominant advantages of Rocephin and the generics were those based on a broad and distinctive antibacterial spectrum, unique pharmacokinetics and favourable safety and tolerability profile; these aspects were naturally already ‘documented’ in the case of the proprietary product and ‘anticipated’ in the case of the generics. Main differences: Rocephin could boast the highest quality and professionalism in all areas: manufacture, sales, information and back-up, plus its reputation and support from doctors, based on a research and clinical record documented in publications stretching back over 20 years; the main strength of the generics was, and of course remains, the low price.

Weaknesses

Neither Rocephin nor the generics could be switched from parenteral to oral treatment; they also shared non-optimal antibacterial activity against anaerobes and staphylococci, and the development of resistance. Both were essentially confined to hospital use, meaning the virtual absence of a doctors’ surgery market. Fewer new studies were likely to be conducted on Rocephin after patent expiry and no significant innovations were to be expected; the problems for generics were limited resources for promotion and support as well as potential manufacturing bottlenecks.

Opportunities

In the case of Rocephin, the main mission was to invest in its strengths: quality, professionalism, trust and support. Besides maintaining the main indications, innovations were important, above all in outpatient care, by promoting outpatient parenteral antibiotic therapy (OPAT). It was essential for the proprietary preparation to secure the backing of key opinion leaders in medicine and microbiology. The opportunities for generics were determined by hospital pricing policies and general healthcare costs.

Threats

The main threats to Rocephin and the generics were, on the one hand, the increasing development of resistance and the resulting more restrictive recommendations for use and, on the other, losses from the successful introduction of new drugs (dwindling
interest, shrinking market share). Increasing concern over drug costs ‘threatened’ the ‘more expensive’ proprietary product; the threat to generics lay in the widespread lack of trust and innovation.

The Task Force drew on these SWOT analyses to develop a 4P (product, position, promotion, price) strategy. They listed the proprietary product’s relevant advantages in all four areas. It was then up to the various Roche subsidiaries to set the priorities relevant to their respective regions (Table 2).

<table>
<thead>
<tr>
<th>The 4P Strategy</th>
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<tbody>
<tr>
<td>1 Product</td>
<td>Efficacy and safety, production and supply</td>
</tr>
<tr>
<td>2 Position</td>
<td>Innovations: packaging, indications</td>
</tr>
<tr>
<td>3 Promotion</td>
<td>Medico-scientific information and support for prescribers</td>
</tr>
<tr>
<td>4 Price</td>
<td>Adjusted pricing</td>
</tr>
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</table>

Product

The emphasis here was on the positive experience garnered on the efficacy and safety of Rocephin since its introduction in 1982. Important features were the seamless production through delivery process, the range of different and more user-friendly packs compared to the generics (250 mg, 500 mg, 1 g and 2 g vials), solvent (for intravenous and intramuscular administration) and single and bulk packs.

Position

For hospital bulk buyers, the price difference between the proprietary product and the generic was more important than for the ambulatory sector, with corresponding pricing consequences. Innovations such as OPAT in particular, with the possibility of intramuscular administration, helped to strengthen the position of Rocephin, as did new indications such as complicated otitis media and long-term osteomyelitis treatment.

Promotion

Promotional strategy was largely dependent on these positioning priorities. The competition between proprietary product and generic greatly downplayed the medico-scientific dimension compared to the price-dominated influence of healthcare management. Besides maintaining a flow of information for everyone, there had to be a certain concentration of medical support, including for research and teaching, for loyal or new buyers of Rocephin. Such changes had to be communicated in a transparent and open manner. It was mandatory for sales representatives to be given a new remit and undergo retraining.

Price

Two important precepts governed the setting of prices and discounts. Customers had a preference for a proven proprietary drug but no loyalty; there had to be no general price reduction on patent expiry since this would prompt misunderstanding and loss of trust. These two precepts, together with regional specificities, governed price policy. Special pack sizes, intramuscular administration and smaller doses for pediatric patients warranted particular attention; as long as only Rocephin offered such advantages, considerable influence could be maintained over customers’ decisions.

Experience taught that once the non-viable generic manufacturers disappeared – as they tended to after a few years – the ‘free-fall’ price slump would come to a halt and revert into a ‘moderate’ upward trend.

Outpatient parenteral antibiotic therapy

Over the last two to three decades, OPAT has spread from the USA to the rest of the world and has become an important mainstay of patient care.

What drives OPAT is the determination to avoid the burdens that go hand in hand with hospitalisation: cost, hospital-acquired (nosocomial) infection and the emotional strain of separation from family and familiar surroundings. Cost savings are mainly in staff and infrastructure. Children and the elderly find it particularly hard to be away from their families and homes; the resulting impairment in quality of life can be measured objectively.
Nosocomial infections are an important and unfortunately growing problem worldwide. Their incidence is increasing, as is the proportion caused by antibiotic-resistant bacteria: in the USA over two million hospital patients annually are infected with resistant organisms, with fatal consequences in around 100,000. These highly dangerous and often highly infectious problem bacteria originate on the one hand from the hospital setting, in particularly from humid fittings such as showers, taps, drains, ventilation and air-conditioning systems and, on the other from human carriers, usually other patients, and less often staff and visitors. The hygiene measures put in place in hospitals – primarily strict disinfection of hands, structural measures and the requisite isolation or decontamination of carriers – are being neglected in the concern to cut staff and investment costs. In addition to hygiene, two further developments are set to aid the battle against nosocomial infection: fast and reliable pathogen identification (rapid diagnostics) and vaccination against resistant bacteria such as Ps. aeruginosa, Clostridium difficile and S. aureus.

The key preconditions for OPAT are efficacy, safety and compliance, established after appropriate scientific study in the relevant indications and patient groups. Patients can be given the antibiotic intravenously or intramuscularly in the outpatient clinic, day hospital, doctor’s surgery or at home. Management is either exclusively ambulatory or begins on an inpatient basis until the requisite improvement takes place. The most important OPAT-responsive infections are those affecting bone, skin and soft tissue, urinary tract, upper and lower airways but also pyrexia of unknown origin and invasive infections such as meningitis, sepsis and endocarditis. A unique well-established instance of OPAT is the Transnet Phelophepa healthcare train in South Africa, a 350-metre long train that has been providing basic medical care for various remote rural populations since 1993.

The distinctive features of Rocephin – potent broad antibacterial spectrum, favourable safety and tolerability profile and once-daily intravenous or intramuscular administration – are decisive contributors to the three relevant aspects of OPAT: efficacy, safety and compliance. Rocephin is an ideal antibiotic for adult and pediatric OPAT. It is the most frequently used antibiotic, followed by teicoplanin, in the majority of OPAT publications.

Site and type of antibiotic administration vary from country to country and from continent to continent, as do the relevant infectious diseases. In the USA, for example, antibiotics are generally administered at home as a short infusion; in most European countries they are given in the hospital outpatient department or day hospital, again intravenously, with the exception of Italy where intramuscular administration is preferred. Outlying medical facilities in many developing countries also usually prefer intramuscular administration.

For OPAT to be accepted and widely disseminated in a given setting – in a word, for it to be successful – it needs to be in the interests of all stakeholders: patients, doctors, healthcare administration and payers. Ongoing professional commitment by the specialists involved – doctors, caregivers, logistic experts – is an essential prerequisite as expectations are high and should not be underestimated.

Current position

Even 30 years after their introduction, Rocephin and the ceftriaxone generics retain an important position in the successful treatment of infectious diseases around the globe. The advantages we have repeatedly emphasised – grounded in the drug’s distinctive antibacterial, pharmacokinetic and toxicological properties
– continue to simplify treatment and, by extension, to provide long-term clinical and cost benefits.

The 4P issues generated by patent expiry and the emergence of generics, the detailed descriptions of resistance development and the determined promotion of new antibiotics by rival companies were all mainly concentrated in industrial countries. Repeated concerns about safety in neonates and the elderly likewise attracted most attention in Europe and North America. The reasons for reticence in using ceftriaxone in neonates, in particular in immature premature babies, were based on its potential to displace bilirubin from its binding to albumin, incurring the theoretical risk of kernicterus and the threat, since confirmed in a total of nine published case reports, of potentially lethal ceftriaxone-calcium complexes forming in the kidneys and/or lungs when ceftriaxone is coadministered intravenously with calcium. In geriatric patients a warning has been issued about the extremely rare reactions of ceftriaxone-induced hemolytic anemia and biliary lithiasis and also the theoretical, although never published, risk of lithiasis in the kidneys and lungs. Neonates and the elderly share some common features when it comes to tissue and fluid and electrolyte balance vulnerability: immaturity at the beginning of life, and aging at its end.

Roche sales figures reveal that in the ranking of sales-generating products, Rocephin slipped from the number one spot (CHF 1.290 bn) in 1998 to 20th (CHF 311 m) in 2010. In 1998 Rocephin accounted for 10% of total sales; by 2010 its share had fallen to under 1%. The biggest drops coincided with patent expiry in Europe in 1999/2000 and in North America in 2005/2006.

In 2010 the breakdown of Rocephin sales was as follows: Asia 30.8%, Japan 20.6%, Western Europe 18.3%, Latin America 15.8%, Central and Eastern Europe, Middle East, Africa and Indian subcontinent (CEMAI) 13.5%, North America 0.5% and other countries 0.5%. China headed the country list (22.9%), followed by Japan 20.6%, Italy 12.2%, Mexico 6.8% and Brazil 3.3%, together with a further 72 countries across all continents.

Interesting concerted efforts are underway in China as part of the 4P strategy to put the case for proprietary Rocephin against more than 100 (!) rival generics. A 30% price reduction in 2011 is due to be more than offset by an average 15% annual increase in sales between 2011 and 2013. The 4P conclusions listed on page 168 will be duly evaluated and addressed: positive experience of the product, its proven position in hospital and ambulatory care,
its promotion among prescribers via medico-scientific support and the above pricing review (30% reduction with immediate effect).

The international sales data compiled by IMS Health using its proprietary MIDAS® data analysis service over the last decade (2000–2010) reflect the developments anticipated by the Task Force. Table 3 shows total ceftriaxone sales, i.e. sales of proprietary Rocephin plus the many generics and also the data for Rocephin alone. In 2000 and 2001 the Rocephin share still amounted to around 85%, between 2002 and 2004 to around 75%, and in 2005 to around 60%. On expiry of the patent rights in North America in 2005/2006, it plunged further to between 30% and 35% between 2006 and 2009. In 2010 Rocephin still accounted for 21%.

Analysis of the total sales figures (proprietary product plus generics) reveals no major changes: CHF 1.3 bn from 2000 to 2002, CHF 1.4 bn from 2003 to 2005, and a plateau of CHF 1.0 bn from 2006 to 2010. Market growth and price slump only mirror each other if total standard units sold are taken into account at the same time: sales more than doubled (+203%), from 122 million standard units in 2000 to 370 million standard units in 2010, corresponding grossomodo to an estimated price reduction from CHF 10.05 to CHF 2.91 per standard unit, i.e. a price drop of almost three-quarters (-71%).

Corresponding data for proprietary Rocephin show a 78% drop in revenue from 2000 to 2010 (Table 3), halving of standard units sold (-49%) and a price reduction of more than half (-57%).

Breakdown of the MIDAS data for the six sales regions gives some interesting results. Table 3 shows the changes over the decade from 2000 to 2010 in total sales (millions CHF and standard units (millions), and the price drop calculated from those figures.

Total sales show little change: from CHF 1.227 bn in 2000 to CHF 1.075 bn in 2010. However, this situation varies considerably from region to region: major slumps in North America (-83%) and Western Europe (-20%), but impressive increases in other regions – absolute increases of CHF +126 m from the Asia Pacific region (South-East Asia, China, Australia, New Zealand) and corresponding percentage increases in Latin America (+161%) and CEMAI countries (+174%).

The substantial, more than double, market growth based on total standard units of ceftriaxone sold – a consequence of the proliferation of the generics – is concentrated above all in Latin America (+513%), CEMAI countries (+344%) and the Asia Pacific region (+236%).

The price slump of almost three-quarters (-71%) is more marked still in North America (-89%), while in the other regions it amounts to around -50%, except in Japan where it is only -31%, but in conjunction with relatively low sales.

**Current spectrum of indications**

Fundamentally the indications for Rocephin/ceftriaxone listed in the Clinical use section (page 161) have undergone little change over the past three decades, although there are naturally certain differences between ‘rich’ industrial regions and ‘poor’ developing regions.

In parallel to the market growth that we have seen concentrated mainly in CEMAI countries, Latin America and the South-East Asia/Pacific region, ceftriaxone is still very often used as empirical (i.e. first-line post-diagnostic) antibiotic therapy or blind therapy (i.e. in the absence of an identified pathogen) for a wide range of serious infections, such as meningitis and sepsis, lung, bone and

![Table 3: Sales (CHF million and million standard units) and price profile 2000-2010 for Rocephin and ceftriaxone generics together (MIDAS Services, IMS Health)](image)

<table>
<thead>
<tr>
<th>Region</th>
<th>Asia Pacific</th>
<th>Western Europe</th>
<th>CEMAI* (excl. Russia)</th>
<th>Latin America</th>
<th>North America</th>
<th>Japan</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2000</strong></td>
<td>209</td>
<td>383</td>
<td>61</td>
<td>39</td>
<td>491</td>
<td>85</td>
<td>1227</td>
</tr>
<tr>
<td><strong>2010</strong></td>
<td>335</td>
<td>308</td>
<td>159</td>
<td>107</td>
<td>85</td>
<td>81</td>
<td>1075</td>
</tr>
<tr>
<td><strong>Change</strong></td>
<td>+126</td>
<td>-75</td>
<td>+98</td>
<td>+88</td>
<td>-406</td>
<td>+37</td>
<td>-152</td>
</tr>
<tr>
<td><strong>Million CHF</strong></td>
<td>+60%</td>
<td>-20%</td>
<td>+161%</td>
<td>+174%</td>
<td>-83%</td>
<td>+84%</td>
<td>-12%</td>
</tr>
<tr>
<td><strong>Million Units</strong></td>
<td>+72%</td>
<td>+12%</td>
<td>+130%</td>
<td>+163%</td>
<td>+9%</td>
<td>+6.9%</td>
<td>+248%</td>
</tr>
<tr>
<td><strong>CHF per std unit</strong></td>
<td>+236%</td>
<td>+45%</td>
<td>+344%</td>
<td>+513%</td>
<td>+168%</td>
<td>+203%</td>
<td>-49%</td>
</tr>
</tbody>
</table>

*CEMAI, Central and Eastern Europe, Middle East, Africa and Indian Subcontinent
abdominal infections, and in immunocompromised patients. Industrialised Western Europe and North America, with only minor market growth, are more reticent, i.e. more targeted, in their use of ceftriaxone. We have already mentioned two of the most important reasons for this, both of which count for much in these countries: the development of resistance and the promotion of new antibiotics. Ceftriaxone use for OPAT (page 169) has major worldwide importance.

Recent reports of experience with ceftriaxone published between 2008 and 2011 confirm the clinical practice described above. The great advantages of ceftriaxone in the treatment of acute bacterial meningitis in children are obvious, in particular in regions with basic medical infrastructure, given a treatment duration shortened from 10 to 5 days. Ceftriaxone has a broad and important role to play in pediatric infectiology in developing countries, in particular for the treatment of bacterial intestinal infections, pyrexia of unknown origin in conjunction with neutropenia and severe acute malnourishment. Recent reports of ceftriaxone in adults confirm positive experience in the treatment of lung and intestinal infections, sexually transmitted disease and febrile neutropenia, as well as in infection prophylaxis following various types of surgery. In particular, these reports have confirmed a reduction in wound infections and nosocomial urinary and pulmonary infections. An interesting study from ten university hospitals in Korea confirmed the practical advantages of ceftriaxone antibiotic treatment when appropriately prescribed and correctly administered.

**Number of patients treated**

141.7 million patients worldwide received Rocephin between its introduction in 1982 and the end of January 2012.

Assuming a mean single daily dose of 1.5 g ceftriaxone (depending on patient weight and disease severity, the daily dose can range from 100 mg to a usual maximum of 4 g), a mean treatment duration of 10 days (once-daily treatment can be given for anything from 1, 3, 7, 10, to 21 days or more depending on indication), and bearing in mind the international sales data (MIDAS® Services, [Table 3], compiled by IMS Health), we can advance the following figures: during the 17 years from 1982 to 1999, 165 million patients were treated with ceftriaxone, including 121 million (73.3%) with Rocephin. In the ensuing 12 years between 2000 and 2011 a total of 215 million patients were treated with ceftriaxone, including 20 million (9.3%) with Rocephin. Hence between 1982 and 2011, 380 million people of all ages – from premature babies, through children and adults to the elderly – benefited from treatment with ceftriaxone, including 141 million (37.1%) with proprietary Rocephin. These impressive figures will keep on growing over the next few years as the success story of Rocephin and the ceftriaxone generics continues to unfold.

**The Brazilian example**

Brazil, currently the largest and most promising country in South America, is of major importance for Roche. It also was, and continues to be, an important region for Rocephin. In late August 2011, the author had the opportunity to analyse the current position of Rocephin in the two cities of Rio de Janeiro and Sao Paulo.
Paulo, each with a multimillion population – six million in Rio and twelve million in Sao Paulo. Rio de Janeiro boasts blue ocean, beautiful beaches, mountains and an appealing joie de vivre. By contrast, Sao Paulo has a gigantic sprawl of high-rise buildings, a bustling business community and tolerant multiculturalism. Roche-Brazil was responsible for organising in remarkably expert detail the author’s many visits to various hospitals and institutes, as well as an informative guided tour.

Country and people. French anthropologist Michel Maffesoli (born in 1944 in the small town of Graissessac in the Cévennes) wrote a few years ago: ‘Brazil embodies emotions and feelings more than almost any other culture; it is a world in which sentiments are used as a buffer against difficulties’. A positive attitude, motivation and an ever-ready smile are the predominant response, no matter how great the problem – Brazil is an authentic, well-balanced and proud land of the future. The democratic political system works, the economy is booming, the currency is stable and environmental awareness is growing.

Prescription drugs. In Brazil the commercial drug climate is extraordinarily harsh, both between the private and public markets, and between proprietary products and generics. Private patients treated mainly in private hospitals account for only around 10% of total pharmaceutical sales. This 10%, however, generates far higher profits than sales for ‘state’-insured patients. The public market encompasses the public hospitals in particular and is under very strict state control.

Each new drug is first introduced onto the private market; registration for general use is complicated, protracted and involves a price reduction of at least 40%. Furthermore, any forecasts about acceptance and position in public hospitals are, as a rule, very unreliable, meaning that by no means all drugs registered primarily for the private market will clear this hurdle. For some years now, the state has demanded that most of the drugs approved for general use be produced in Brazil. This encourages technology transfer within private-public partnerships. It guarantees that manufacture and control are of the same high standard as in the country of origin; relocation is offset by prolongation of the patent term by up to 5 years.

Many of the very numerous, if not countless generics in Brazil are sub-standard despite state control efforts. This applies...
in particular to the active pharmaceutical ingredient (API), i.e. to efficacy. Many such APIs originate from dubious sources in Asia, above all India and China. The potential disadvantages for patients are therefore substantial. In some cases they can be life-threatening if the unwittingly underdosed generic has no therapeutic effect.

In most public hospitals price is the sole factor determining the choice of drug, meaning that state-insured patients virtually never receive anything but generics. This naturally applies to ceftriaxone too.

Hospitals. There are huge differences between private and public hospitals in Brazil in terms both of building fabric and space as well as organisation and administration. Many private clinics offer patients all the comforts of a luxury hotel, whereas conditions in public hospitals can be a cause for concern. The training, appearance and motivation of the administrative staff – and by extension all processes and procedures – are noticeably better in private than in public hospitals. Nonetheless, the nursing staff and in particular the doctors go about their work in an excellent and highly committed manner in all hospitals.

Rocephin. In 2011 annual cephalosporin sales in Brazil totalled just under BRL (Brazilian reals) 400 m, accounting for 1% of total drug sales. Cephalosporins were no exception to the general rule that state-insured patients account for approx. 90% of sales. Thus generics outweighed proprietary drugs to the same degree (approx. 90%).

The share of proprietary ‘Rocefin’ in Brazilian ceftriaxone sales still amounted to around 10% in 2011 (4th place) in terms of Brazilian reals and around 20% (3rd place) in terms of total standard units sold. Of course, this ‘discrepancy’ in percentage shares is not explained by cheaper standard unit prices for Rocefin
but by the fact that the proprietary product – unlike most of the total 15 generics – is also sold in small packs, both in terms of number of doses and dosage strength for pediatric patients.

**Position in the clinic.** Proprietary Rocefin and the ceftriaxone generics enjoy strikingly high status in Brazil almost three decades after their introduction in 1985, in both public and private hospitals. They are also the first-line choice of antibiotic for treating serious invasive bacterial infections, in particular where there is a suspicion or confirmation of meningitis, sepsis and lung infections, but also for treating as yet unidentified conditions, alone or in combination with other antibiotics. In this connection it is worth citing two Brazilian infectiologists:

- **Young doctors’ favourite rule of thumb:** ‘Pelo sim, pelo não – Rocefin!’ which roughly translates as: ‘If in doubt – Rocephin’!
- **The position of Rocefin/ceftriaxone in the extended antibiotic family is that of a mature young adult!**

Rocefin/ceftriaxone is also very often given in OPAT, both intravenously and intramuscularly.

All infectiologists, internists and pediatricians interviewed about the efficacy of Rocefin/ceftriaxone described it as being highly reliable, very safe and very easy to use.

Thirty years after launch, Rocephin and the ceftriaxone generics continue to offer impressive and lasting medical and economic advantages in the successful treatment of the most diverse infectious diseases in both pediatric and adult patients worldwide.

### Acknowledgments

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